





# SAJOUS'S ANALYTIC CYCLOPEDIA OF PRACTICAL MEDICINE

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SUPPLEMENT



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# PREFACE

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IN accordance with a well established policy, the Publishers and Editors of the CYCLOPEDIA OF MEDICINE, SURGERY AND THE SPECIALTIES each year bring out a Service Volume designed to supplement the original work. This has proved effective in bringing up to date the extensive material in the Cyclopedia and in placing at the disposal of its readers, in convenient form, information about the rapid advances that mark the ever changing trends in medical progress. The Service Volume is not a systematic review of current medical literature. Its purpose is to furnish additional data on those subjects that appear in the Cyclopedia which, because of recent noteworthy changes and advances, require supplementing and to introduce new material which has become available since the publication of the Cyclopedia.

In the preparation of this volume the Editorial Board and the Associate Editors of the Cyclopedia decided which subjects were most in need of amplification and what new material should be added. In some instances, the Associate Editors themselves provided the supplementary material. On the other hand, a large proportion of the reviews that make up this volume has been contributed by the authors originally responsible for the Cyclopedia articles. By following such a plan, greater continuity and uniformity in the treatment of the various topics have been maintained.

The format of this Service Volume is similar to that found in the Cyclopedia. The various topics have been arranged alphabetically, thereby making it easier for the reader to locate any desired subject. Under the main headings of Medicine and Surgery, the various well recognized sub-specialties will be found grouped alphabetically. It is believed that this new arrangement will prove more satisfactory than that adopted in earlier Service Volumes.

The contributors, all of whom are outstanding in their various special fields of Medicine and Surgery, have brought to their tasks excellent critical judgment and have endeavored to emphasize only those points that are of acknowledged, proved value. Throughout the volume an effort has been made to stress particularly diagnosis and treatment.

Attention should be drawn to certain subjects which, because of their timeliness, should prove of particular interest. In this group fall Aviation Medicine and War Surgery. Therapeutics, in its broadest sense, is emphasized throughout the volume. Under this heading are included such subjects as Physical Therapy and Shock Therapy. Dietotherapy has been made part of the section on Gastroenterology in which are also included an important discussion of Vitamins; the

newer aspects of Endocrine Therapy have not been neglected, and under the section on Therapeutics will be found a critical discussion of some of the newer drugs, such as Heparin, Histamine, the Sulfonamides, Nicotinic Acid and many other preparations that are engaging the attention of the medical profession. Under Radiology have been introduced several original articles on subjects that, because of their newness, could not have been included in the Cyclopedia, such as the Cyclotron and Neutron Therapy as well as an article on Body Section Roentgenography. The sections on Cardiovascular Disorders, Hematology, Otorhinolaryngology, Neurosurgery and Pediatrics, especially Infant Feeding, are unusually complete and should prove of great practical value because of the care with which the subject matter has been selected and the thorough and authoritative way in which it has been treated.

The thanks of the Editor are due to the Editorial Board and the many contributors whose zeal and co-operation have made this volume possible. Again, he wishes to express his appreciation to Dr. Edward L. Bortz, the Assistant Editor, who is largely responsible for planning the volume, and to gratefully acknowledge the faithful work of Miss Louise I. Weisgerber, who prepared the manuscripts and saw the volume through the press. Thanks are due also to Dr. Frederick C. Smith for his careful work in the preparation of the index. The Publishers are to be congratulated upon the pleasing appearance of the book and the liberal way in which it has been illustrated.

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# The Cyclopedia of Medicine

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## BACTERIOLOGY

Edited by CLAUDE P. BROWN, M.D.

### BLOOD CULTURES

By CLAUDE P. BROWN, M.D.

Invasion of the blood stream by bacteria either through an open wound or inflammatory process is not a common occurrence, but is fraught with great danger to life when it occurs.

The selective growth characteristics of bacteria therefore continue to arouse interest and papers appear in the literature outlining newer methods of approach, directed mostly toward satisfying these requirements.

Immunity acquired by the human body commences in fetal life and continues after birth as exposure occurs to bacteria or to the by-products of bacterial metabolism.

The immunity thus acquired may not, however, give adequate protection, because of its short duration or because some bacteria have inherent invasive characteristics, which may build up rapidly in passage from person to person. On the other hand, many persons undoubtedly acquire a resistance to invasion of the blood stream.

This is well illustrated by the typhoid "carrier" who harbors pathogenic bacteria, but is personally immune. The victim of hemolytic streptococcic bacteremia who recovers does not usually become a constant source of infection,

while the one with endocarditis due to *streptococcus viridans* may continue to have foci of infection which constantly menace life.

It thus readily can be seen why the problem of blood cultures continues to receive much attention. There probably are several reasons, *i.e.*, the culture media used, the time factor or day of the disease, and the frequency of taking them. The culture media must be capable of supporting the bacteria which are most commonly invasive as well as those more rarely found, along with the selection of the proper culture material, the physical conditions likewise must be considered, such as the possibility of the organism requiring the presence of CO<sub>2</sub> or even anaerobiasis. From time to time the question is raised as to the importance of complement in the blood and whether its presence would assist complete phagocytosis with destruction of the bacteria, particularly if only a few organism were present.

There can be no objection as to the use of substances in the culture media which will absorb or render complement inactive, providing such substances do not inhibit bacterial growth. The Reviewer has found that a small amount of agar (0.1 per cent) answers the purpose; however, it is difficult to see how

the presence of complement *in vitro* will influence growth, since it has not occurred *in vivo*, otherwise blood cultures would in all probability more often be negative, besides in some diseases there is a deficiency of complement.

A single blood culture, if negative, should be repeated once or more times if there is the slightest reason to believe a positive culture might be obtained.

The *time* of taking the culture may be of very great importance; early cultures are advisable, certainly those having a chill followed by a rise of temperature should by preference have blood cultures taken about the time of the rise, rather than at the peak or when subsiding.

Butler believes that for routine blood cultures 4 media are required: Tryptic broth (Hartley's modification); anaerobic tryptic broth; glucose broth (Wright) with trypsin, and nutrient agar, and in the case of enteric fever, bile or bile broth, 5 to 10 cc., should be added. She advises that 10 cc. of blood be taken and immediately distributed to 3 of the media, 3 to 4 cc. into tryptic broth, 2 to 3 cc. into anaerobic tryptic broth, 1 cc. into glucose broth agar.

### Preparation of Media for Blood Cultures

**Hartley's Modification of Douglas's Tryptic Broth**—Obtain 150 grams of veal or other suitable meat, free from fat, and mince. Mix with 250 cc. of tap water and heat to 80° C. in the steamer. Add 250 cc. of 0.8 per cent sodium carbonate solution (the anhydrous salt), cool to 45° C., and add 5 cc. of Cole and Onslow's pancreatic extract, and 5 cc. of chloroform. Mix thoroughly and incubate at 47° C., shaking frequently until the biuret test gives a pink coloration (usually in from 3 to 6 hours). Add 40 cc. of N 1 hydrochloric acid and heat in the steamer for 30 minutes. Cool, filter through paper, adjust the reaction to pH 7.6, and distribute in 100-cc. quantities in Florence flasks of 250-cc. capacity. Sterilize by placing in the autoclave and maintaining a current of

steam for 1 hour, then raise pressure slowly to 10 lbs. and turn off the steam.

**Cole and Onslow's Pancreatic Extract**—Obtain pig's fresh pancreas, free from fat, weigh and mince finely. Add 3 times the weight of distilled water and once the weight of absolute alcohol. Place the mixture in a large bottle, shake thoroughly and allow to stand at room temperature for 3 days with occasional shaking. Strain through muslin and filter through a large folded filter paper. Add 1 cc. of concentrated hydrochloric acid to each liter of filtrate, allow to stand for a few days, and filter off the sediment. Store in a stoppered bottle in a cool dark place.

**Anaerobic Tryptic Broth**—Free from fat, and finely minced veal or bullock's heart. Steam for 1 hour and allow to dry. Fill test-tubes ( $\frac{3}{4}$  inch diameter) to a depth of  $\frac{1}{2}$  to  $\frac{3}{4}$  inch. Sterilize by autoclaving for 20 minutes at 15-lbs. pressure. Prepare tryptic digest broth as above, but adjust pH to 7.8 and add 12 to 15 cc. to the cooked meat. Stand the tubes in boiling water for 10 minutes (the meat should remain at the bottom of the tube), add melted paraffin (previously sterilized in the autoclave) to a depth of  $\frac{1}{2}$  inch, and sterilize as for tryptic broth. Retest the pH of the clear broth, which should not be below 7.2. The paraffin used should have a melting point of 45° to 50° C. Immediately before using, stand the tubes in boiling water for 10 minutes to expel any dissolved air, cool rapidly and add 0.5 cc. of sterile trypsin (Fairchild's *injection trypsin*) to each tube. If the tubes are not used at once, they should be stored in the cold. This storage is to be avoided whenever possible.

**Glucose Broth (Wright) with Trypsin**  
To 1 liter of distilled water add 10 grams of peptone, 5 grams of sodium chloride, and 500 grams of meat, preferably veal, finely minced after removal of excess of fat. Mix well and heat for 20 minutes at 68° C., stirring at intervals. Shake well and steam in the steam sterilizer for 30 minutes, filter through paper, and adjust the reaction to pH 7.8 to 8.0. Again steam for 30 minutes and filter through paper. Check the reaction of the filtrate (pH 7.6 to 7.8) and add 1.5 grams of glucose per liter. Tube in 7- to 8-cc. quantities and sterilize by autoclaving for 10 minutes at 10-lbs. pressure. Immediately before using the glucose broth (Wright) add 0.5 cc. of sterile trypsin to each tube.

**Nutrient Agar**—Prepare broth according to Wright's method, but omit the glucose. Dis-

solve in it 2 per cent of agar, clear the resulting mixture with egg white, tube in 12-cc. quantities, and sterilize by autoclaving for 10 minutes at 10-lbs. pressure. The broth should not be sterilized before the addition of the agar.

**Ox Bile**—Obtain bile from the abattoirs. Autoclave for 20 minutes at 15-lbs. pressure, filter through paper, tube in 10-cc quantities, and sterilize by autoclaving for 20 minutes at 15-lbs. pressure.

**Bile Broth**—Mix equal parts of broth as used for nutrient agar and ox bile prepared as above. Tube 10 10-cc. quantities and sterilize by autoclaving for 20 minutes at 15-lbs. pressure.

The plugs of all tubes and flasks should be protected with well-fitting rubber caps to protect them from dust and to prevent evaporation of the medium. The media should be stored in a cool dust-free atmosphere, if possible in a cold room.

If bile broth is used in suspected cases of enteric fever, then an additional 5 to 10 cc. of blood should be withdrawn and added to the medium.

When using the anaerobic tube, it should be heated around the site of the paraffin so that the paraffin will float when tipped sidewise, permitting inoculation of the broth.

### New Method of Blood Culture in Undulant Fever

In reporting on the treatment of undulant fever with sulfanilamide, Kleeberg, Gurevitch, and Alkan,<sup>1</sup> state that

they have obtained positive blood cultures in 9 out of 11 cases, 5 of which were positive in the 6 cases observed.

The culture medium used was semi-solid, consisting of

Agar broth, 1:7

Glycerin, 3 per cent

Prim. phosphate of potassium, 0.05 per cent

Sec. phosphate of sodium, 0.15 per cent

Cystin, 0.01 per cent

Tube, 8 to 10 cc.

Sterilized at 15-lb pressure for ½ hour pH 7.2 to 7.4.

In every case under examination 2 cc. of the patient's blood is added to 1 or 2 test tubes, which are then incubated for 48 hours at 37° C. After 48 hours' incubation the contents of the culture are inoculated on 6 per cent glycerin agar. This procedure is repeated daily, always inoculating from the first culture on the same 6 per cent glycerin agar.

*Brucella*, as a rule, grows slowly. On an average, the cultures did not become positive until the tenth to twelfth day. In view of the protracted course of the disease, however, this slow growth is of no importance. On the glycerin agar *brucella* forms small translucent colonies which, during the first days, are often scarcely recognizable. From the eighth day, therefore, the colonies should be subjected to microscopic examination. Diagnosis is corroborated, apart from the typical microscopic picture, by agglutination against immune serum.

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## MORGAN BACILLUS

By CLAUDE P. BROWN, M.D.

Pulaski and Dietz<sup>2</sup> again draw attention to the rôle of Morgan's bacillus as the causative agent in infections. They report the case of an adult, 25 years of age, who developed a fatal septicemia, the blood culture being positive for *Bacillus Morgani*. The same organism

was recovered from the ear, apparently the original source of the infection, which followed a "hot" spark burn from an acetylene torch.

The sputum later was positive as was also a culture from an abscess in the neck.

## PNEUMOCOCCUS

By RANDLE C. ROSINBERGER, M.D.

In the study of pneumonia due to the pneumococcus, a specific diagnosis regarding the type of the infecting organism and the treatment of the case is necessary today.

It is a well-known fact among bacteriologists that there are 33 different types of pneumococci; pneumonia may be due to any one of these. Typing of the causative organism may be done in several ways, *i. e.*, by the *mouse method*, by the *Avery method* and today more commonly by the *slide method* known as the Neufeld reaction. The advantages of typing the organism is to treat the infection specifically, *i. e.*, with an antiserum obtained from a horse or rabbit.

The slide method is briefly as follows:

Take a small mass of sputum on a glass slide and mix with it a drop of a serum and a drop of dilute methylene blue. Cover with a cover-glass and examine with oil immersion lens. If the reaction is positive, the capsule on the pneumococcus will be observed to be greatly swollen and the organism stained a delicate blue. It has also been suggested that after the sputum and serum are mixed, the mixture be dried after 30 minutes, gently heated over a flame. Methylene blue is then added for a minute, washed off, dried and examined with oil immersion lens. The capsules responding to the action of the specific serum will be seen to be greatly swollen.

For the laboratory worker or physician to use each of the 30 odd serums for typing process would be an endless procedure. It has been found that these typing serums can be suitably grouped into 6, lettered A, B, C, D, E and F, each lettered serum representing from 3 to 6 types of pneumococci.

For example, if group "A" serum gives a positive reaction with sputum it represents types 1, 2 and 7; while if group "D," it means types 10, 11, 13, 20, 22 and 24 have reacted. If one of

these typing serums gives a group reaction, then further tests must be made to determine the specificity of the infecting organism.

Having obtained the type of infection, the case can now be treated with a specific serum and best results seem to be obtained by using antiserum from the rabbit. Before treating a case with serum, an intradermal or conjunctival test should be performed to determine sensitivity against the foreign protein represented by the therapeutic serum.

Regarding the treatment of *croupous pneumonia* by *antiserum*, the dose should be given intravenously. This dose should be proportionate to the severity of the disease and blood cultures should be taken as a guide as to the prognosis of the case. Where a bacteriemia is present, a larger dose or successive doses of the remedy should be recommended.

It is recommended by some that a *skin test* devised by Francis be used to determine whether enough antipneumococcus serum has been injected. The specific pneumococcus polysaccharide is used for the test and the immediate wheal and erythema are due to the local union of antibody and polysaccharide and indicate the presence of type specific antibodies in the blood. It is claimed that no patient who failed to show a positive skin reaction recovered from pneumonia.

As in the treatment of a case of diphtheria by 1 large dose of antitoxin, so an effort is being made to obtain a similar result in pneumonia by giving 1 large dose, say 50,000 to 100,000 units, instead of several smaller doses.

It has also been suggested that *epinephrine solution* 1:1000 should be held ready for emergency.

TYPING OF TYPHOID BACILLI WITH TYPE II V<sub>i</sub> PHAGE

By JAMES CRAIGIE, M.B., Ch.B.

The method of typing strains of *B. typhosus* introduced by Craigie and Yen<sup>3, 4</sup> (1938) is based on observations on the variation of 1 of 4 known species of specific V<sub>i</sub> bacteriophages, while its practical application depends on the stability of the types thus demonstrated. Extensive epidemiological and laboratory observations have established the essential stability of the main types in the chronic carrier, in the course of the natural transfer of the organism in human infections, and under a variety of conditions of *in vitro* culture and transfer<sup>4, 7-9, 11</sup>. The method consequently provides the epidemiologist with a means of determining whether a group of apparently related cases are common-source infections and of excluding carriers, excreting a given type, from further consideration as sources of infection in an outbreak in which a different type is implicated. For example, if a case of type F infection occurred, a source of type F infection should be sought for, regardless of any evidence of contact with a type E carrier. The reader is referred to papers by Craigie and Yen,<sup>4</sup>

Yen,<sup>11, 12</sup> Brandon,<sup>13</sup> and Lazarus<sup>5</sup> for examples of the epidemiological application of the typing method. It is suggested that on occasions the task of the epidemiologist may be facilitated if records were available regarding the type excreted by every known carrier in the area.

**Vi Phages**—This term is applied to species of phage which attack only V form strains of *B. typhosus*, *i. e.*, strains which elaborate the Vi or virulence antigen, exhibit resistance to O agglutination during the logarithmic phase of growth and are specifically agglutinated by pure V serum. The nonvirulent W form to which the V form degrades on repeated subculture is not sensitive to these phages. Four species of specific Vi phage are known.

**Identification of V Form of *B. Typhosus***—Since specific Vi phages are employed in typing, only the V form of *B. typhosus* can be typed. Freshly isolated strains of *B. typhosus* are nearly always V form cultures. However, strains isolated some time previously or strains isolated from specimens

TABLE I

V <sub>i</sub> Phage	Relative Particle Size	Thermal Death-point (30 min)	Neutralization by Antiphage Serum				Lytic Activity for V Forms of <i>B. typhosus</i>
			I	II	III	IV	
Type I .	Large phage	67-70° C.	+	-	-	-	Lyses all V forms*
Type II .	Medium phage	69-72° C.	-	+	-	-	Develops a high selective lytic activity for the type of <i>B. typhosus</i> on which it is propagated.
Type III..	Small phage	61-64° C.	-	-	+	-	Lyses majority of V forms
Type IV	Medium phage	59-62° C	-	-	-	+	Lyses majority of V forms with exception of type F (Rawlings-Watson) and D <sub>1</sub> .

\* Except type M.

containing Vi phage may be W form cultures and cannot be typed unless the V form is recovered and isolated. A test with a mixture of type I and type IV phages (Craigie, 1940)<sup>8</sup> will indicate whether a culture is pure V form, W form, or mixed culture and may be conveniently combined with a preliminary typing test (see below). The plaques produced by type I phage on type M strains are very minute and may be abnormally small on some type A and type E strains. Consequently, high concentrations of this phage may be required to produce confluent lysis on such strains. Type IV phage is fully active and produces normal plaques on types A and E, while type F and some other types which are insensitive or less sensitive to phage IV are fully sensitive to phage I.

V form strains which are sensitive to phage I, phage IV, or both, fall into 2 groups, one of which is insensitive to phage II and has been designated as the imperfect V form group

Form of <i>B. typhosus</i>	Susceptibility to Phages I & IV	Susceptibility to Phage II
Typical V form	Sensitive	Sensitive
Imperfect V form	Sensitive	Resistant
W form	Resistant	Resistant

The observations of Yen,<sup>7</sup> Lazarus<sup>5</sup> and the writer<sup>8</sup> show that the average incidence of imperfect V form strains is 10 per cent of all V form strains. The frequency is rather greater in chronic carriers and some instances of change to the typical V form, when a carrier has transmitted the infection, have been observed. Studies in progress suggest the imperfect V forms may be classified and their relationship to the typical V forms determined by other methods.

**Isolation of V Form of *B. Typhosus***—When it is necessary to attempt to isolate the V form from a degraded culture, the following procedure is recommended:

A broth culture is incubated at 37° C until a density of approximately 10<sup>9</sup> bacilli per cubic centimeter is reached, and then centrifuged sufficiently to yield a clear supernatant. A loopful of the supernatant is inoculated into a second tube of broth which is in turn incubated and centrifuged. The supernatant is plated on nutrient agar and incubated overnight. The isolated colonies obtained are examined with a hand lens under oblique illumination from a desk lamp for differences in opacity. Under such lighting V form colonies show a greater apparent opacity than W form colonies (Craigie and Brandon, 1936). Inspissated egg medium (1 part whole egg to 3 parts saline) is recommended for the maintenance of V form strains and particularly for the conservation of the type strains. The medium should be inoculated with a single streak and too long incubation at 37° C is to be avoided.

**Selective Affinities of Preparations of Type II Phage** Type II Vi phage develops a high selective affinity for the type of *B. typhosus* on which it is grown. If subsequently transferred to another type, it acquires an affinity for the new type and loses its affinity for the previous type. In general, the changes in selective affinity brought about by changing the substrate strain of *B. typhosus* are abrupt and complete, but phage propagated on some of the B and D subtypes tends to retain an affinity for these subtypes and is thus unsuitable for the preparation of standard typing preparations. The hypothesis which best explains at present the observed behavior of type II phage is that this phage exists as a series of mutants, each of which attacks a single type of *B. typhosus* and cannot propagate on other strains of this organism. This hypothesis also predicates that this phage exhibits constant mutation rates (Craigie, 1940).<sup>6</sup>

The production of typing preparations of type II phage and their application in the typing method is explained most readily in terms of this hypothesis. If type II phage is propagated on a type E strain of *B. typhosus*, the E mutant of the phage is specifically propagated. However, since the phage mutates, heterologous mutants appear as the phage multiplies, the ratios of each mutant to the homologous mutant and to each of the other heterologous mutants, being constants. Consequently, a type II phage preparation containing over  $10^7$  phage particles will contain most mutants and thus attack most types. However, if a series of dilutions of the phage are examined it will be found that in the higher dilutions the activity of the phage is restricted to the homologous type. It is the higher, specific dilutions of phage which are used in typing. If, however, it is necessary to prepare phage for a heterologous type for which no phage is available, a concentration of phage sufficiently great to yield the desired mutant is required. For example, the F mutation rate is approximately 1 to  $10^7$ , this figure representing the ratio of this mutant to the mutant which has been selectively propagating on the substrate strain of *B. typhosus*. To initiate growth of type II phage on type F, starting with a heterologous phage preparation, it is therefore necessary to employ a concentration of phage containing at least  $10^7$  homologous mutant phage particles and therefore at least 1 F mutant phage particle. Once selective propagation of this F mutant on type F has been initiated, further propagation proceeds without difficulty and the other mutants present in the original volume of phage, unable to propagate on type F, become diluted out as dilutions are made in the course of

further propagation, until the low ratios representing their mutation rates are established.

The technical details of making typing preparations of type II phage are described in a previous article (Craigie and Yen 1938).<sup>3</sup> These will not be referred to here, since typing phage preparations which have been the subject of extensive studies are at present available from the author, if it is desired to have the results of routine typing based on a common set of standards. The ultimate standards are, of course, not the phage preparations, but the type strains on which they have been propagated.

**Method of Setting Up Typing Tests**—The following description is quoted from a previous article<sup>3</sup>:

In typing *B. typhosus* with phage II or in subjecting the culture to a preliminary test, a plate method is used. While the technic of carrying out these tests is simple, a strict attention to certain details is essential. In brief, the technic is designed to obtain areas of uniform inoculation of the strain on an agar plate on which standard volumes of the phage preparations are superimposed as soon as possible after inoculation and without significantly disturbing the uniformity of bacterial distribution. The nutrient agar plates\* which are used for the tests must be free from defects which, causing irregularities in the thickness of the medium, will result in uneven growth of different areas of the culture being tested. The plates are dried at 37° C. to an optimum degree on setting and are then stored in the cold room. Insufficient drying causes delay in setting up the tests and excessive drying results in uneven distribution of culture and phage.

Two standard platinum loops, 2.75 mm. in internal diameter, No. 20 B & S gauge wire, are used alternately to apply the culture and phage to the plate. These are mounted on long handles, the balance of which may be improved with advantage by weighting. While one loop is actually in use, the other is cooling after sterilization. In transferring a loopful of broth culture to the plate, the loop is used

\* Beef extract-peptone broth in 1 per cent agar, pH adjusted to 7.8.

merely to direct the natural spreading of the broth and should not be rubbed over the agar. The shank of the loop is angled so that the loop will lie parallel with the agar surface during inoculation, the loopholder being grasped between the thumb and first 2 fingers like a pen. A full loopful of broth culture is obtained by sharply moving the culture tube so that the loop quickly breaks the surface of the fluid. Then with the holder held in the way described and with the forearm and side of the hand resting on the bench, the loop is lowered until the drop held in it touches the surface of the agar. At this point, the loop is given a slight horizontal circular movement by moving the fingers, guiding the spreading of the drop over an area approximately 15 mm in diameter. A number of areas, corresponding to the number of phage preparations used in the test, are inoculated with each strain. When the agar has absorbed the fluid which has been applied (optimum 5 to 10 minutes), the phage is applied from the standard loop to the center of the inoculated area. In this case the loopholder is best held horizontally between the thumb and fingers, these pointing downward with the side of the arm resting on the edge of the bench. The loopful of phage is lowered until it almost touches the surface of the agar, when slight rotation of the loopholder will move the loop into a vertical plane, thus allowing its contents to flow onto the center of the inoculated area. It is to be noted that the drop of phage must be allowed to spread naturally on the plate, and the actual contact of the loop and inoculated area is to be avoided as far as possible.

When the fluid which has been applied has dried sufficiently to permit of the plates being safely moved, they are incubated for 2 hours at 37° C. and transferred to the cold room overnight. They are returned to the incubator and are ready for reading in 4 to 6 hours. It should be noted that the plates must not be stacked, since at temperatures significantly below 37° C., *B. typhosus* will grow without exhibiting lysis with Vi phage. The method of interrupted incubation has 2 advantages. It permits the phage reactions to be observed at their optimum and before they are obscured by late growth in the case of some strains. Further, the intermediate period in the cold room permits diffusion of the phage into the surrounding normal culture, thus enhancing the clarity of the reactions. The reactions are

best observed by oblique artificial illumination and against a dark background.

Fig. 1 illustrates the results obtained.

**Standardization of Phage for Typing**—For the purpose of typing *B. typhosus* type II phage preparations are used in standardized dilutions referred to as the *critical test concentrations* (C.T.C.). The C.T.C. is the highest dilu-

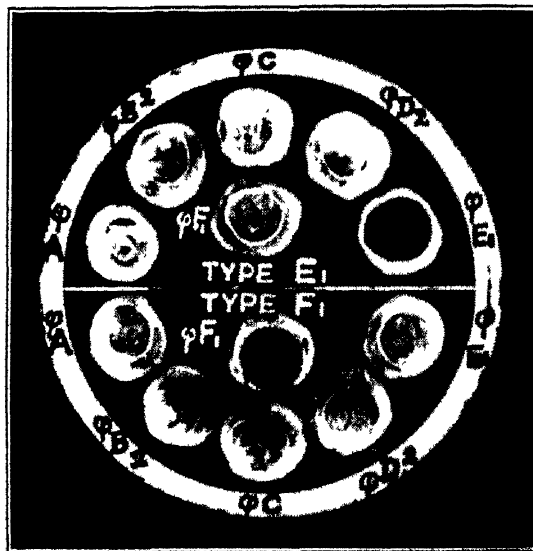


Fig. 1—Phage typing of *B. typhosus*. Photograph of reactions obtained on testing type E<sub>1</sub> and type F<sub>1</sub> strains with the C.T.C. of φA, φB<sub>2</sub>, φC, φD<sub>2</sub>, φE<sub>1</sub>, and φF<sub>1</sub>.

tion of the phage which just produces confluent plaques on the homologous type of *B. typhosus* under the conditions of the test. Confluent lysis of a strain by the C.T.C. of a given phage preparation depends on 2 factors:

- (a) Initiation of plaques by practically all the phage particles present in the standard loopful of the phage C.T.C.
- (b) Development of the plaques so initiated until they become confluent.

Use of unsuitable agar or an insufficient depth of agar will result in growth of the culture being checked before the plaques can attain their maximum size.



On the other hand, an excessively moist or deep agar may result in the plaques becoming overgrown on prolonged incubation.

The critical test concentration of a type II phage preparation is determined by testing standard loopsful of a series of tenfold dilutions of the phage in nutrient broth on the homologous type strain of *B. typhosus*. Twofold dilutions of the highest dilution yielding confluent lysis are then tested to determine the critical test concentration exactly. This test should be carried out under exactly the same conditions as those used in the typing routine.

When the C.T.C. is determined, each of the stronger concentrations which have been prepared may be brought to a tenfold multiple of the C.T.C. by the addition of the requisite volume of broth. This will give a convenient series of concentrations of each phage from which further supplies of the C.T.C. or any desired polyvalent pool of the phages may be made. Further supplies of the C.T.C. are prepared, when required, from the C.T.C.  $\times 10$ , and checked, of course, on the homologous type. The various concentrations of the phages should retain their activity, even in high dilution, for a prolonged period in the refrigerator, but the critical test concentration preparations should be checked at intervals on the homologous type of *B. typhosus*.

**Identification of Types of *B. Typhosus***—A strain of *B. typhosus* is typed by identifying the standard phage preparation which, in its C.T.C., produces confluent lysis. Disregarding, for the moment the subtypes, the reactions which occur conform to the simplified schema shown above.

With the exception of the reactions obtained with type A, which is completely sensitive to all preparations of

Type of <i>B. typhosus</i>	C T C of Phage II					
	$\phi A$	$\phi B$	$\phi C$	$\phi D$	$\phi E$	$\phi F$
A	CL	CL	CL	CL	CL	CL
B	+	CL	+	+	+	+
C	—	—	CL	—	—	—
D	—	—	—	CL	—	—
E	—	—	—	—	CL	—
F	—	—	—	—	—	CL

CL = Confluent lysis

type II phage, and with the B subtypes, which show degrees of modified sensitivity, the C.T.C. of a given phage preparation produces confluent lysis only on the homologous type of *B. typhosus*. The identification of type is complicated, however, by the existence of subtypes of types B, D, E and F. The reactions of all the types and subtypes to the C.T.C. of the standard is given in Table II.

It will be noted from the table that heterologous phage preparations may produce isolated plaques on some of the types and subtypes. Such reactions are obviously different from the reaction of confluent lysis on which type identification is based and should cause no confusion as regards identification of the types and subtypes referred to in the table.

Typing, however, is not such a tedious or time-consuming procedure as Table II might suggest at first sight. It is not necessary to test a strain with all phage preparations for the purpose of type identification. Further, in a given locality over a period of time, only a restricted number of given types and subtypes may be encountered. Once the frequency of isolation of the various types in a given area is known, the sequence of testing for types may be arranged to

TABLE II  
CRITICAL TEST CONCENTRATIONS OF PHAGE (STANDARD PREPARATIONS)

Type of <i>B. thyphosus</i>	$\phi A$	$\phi B_1$	$\phi B_2$	$\phi B_3$	$\phi B_4$	$\phi C$	$\phi D_1$	$\phi D_2$	$\phi D_3$	$\phi E_1$	$\phi E_2$	$\phi F_1$	$\phi F_2$	$\phi G$	$\phi H$	$\phi J$	$\phi L$	$\phi M$	Observed Frequency of Type
A	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	CL	Common
B <sub>1</sub>	$\pm m$	CL	$\pm m$	$\pm m$	$\pm m$	$\pm m$	-	-	-	-	$\pm s$	$\pm m$	$\pm m$	$\pm m$	$\pm m$	-	$\pm m$	$\pm s$	Common
B <sub>2</sub>	$+++$	-	CL	-	-	-	-	-	$\pm m$	-	-	$\pm m$	-	-	$\pm m$	-	-	$\pm m$	Common
B <sub>3</sub>	$+++$	-	$+++$	CL	SCP	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	$+++$	Rare
B <sub>4</sub>	-	-	-	$+++$	CL	$\pm m$	-	-	-	-	-	$\pm m$	-	$\pm m$	$\pm m$	$\pm m$	-	$\pm m$	Rare
C	$\pm n$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	CL	$\pm s$	$\pm s$	$\pm s$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	$\pm n$	Common
D <sub>1</sub>	-	-	-	-	-	-	CL	CL	-	-	-	-	-	-	-	-	-	-	Common
D <sub>2</sub>	-	-	-	-	-	-	-	CL	-	-	-	-	-	-	-	-	-	-	Rare
D <sub>3</sub>	-	-	-	-	-	-	CL	$+++$	CL	-	-	-	-	-	-	-	-	-	Rare
E <sub>1</sub>	-	-	-	-	-	-	-	-	-	CL	CL	-	-	-	-	-	-	-	Common
E <sub>2</sub>	-	-	-	-	-	-	-	-	-	-	CL	-	-	-	-	-	-	-	Rare
F <sub>1</sub>	-	-	-	-	-	-	-	-	-	-	-	CL	CL	-	-	-	-	-	Common
F <sub>2</sub>	-	-	-	-	-	-	-	-	-	-	-	$\pm n$	CL	-	-	-	-	-	Rare
G	-	-	-	-	-	$\pm n$	-	-	-	-	-	$\pm n$	-	CL	-	-	-	-	Rare
H	-	-	-	-	-	-	-	-	-	-	-	$\pm n$	$\pm n$	-	(L)	-	-	-	Rare
J	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(L)	-	-	Rare
Not assigned																			
L	-	-	-	-	-	$\pm n$	-	-	-	-	-	-	-	-	-	-	(L)	-	Rare
M	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	(L)	-	-	Rare

CL = Confluent lysis.  $\pm$  = A few plaques usually present.  $+++$  = Numerous plaques.  $n$  = Normal plaques.  $s$  = Small plaques.  $m$  = Minute plaques

TABLE III  
 SUGGESTED PROCEDURE FOR TYPING *B. Typhosus*

$\varphi B_2$	$\varphi D_2$	$\varphi E_2$	$\varphi F_2$	$\varphi I$ + $\varphi IV$	Polyvalent $\varphi(C.T.C.)$ $B_4, G, H, J,$ $L, M$	Further Procedure
—	—	—	—	CL	—	Test with conc. polyv. $\varphi s B_4, G, H, J, L, M$
—	—	—	—	—	—	
—	—	—	—	—	CL	Test with $\varphi M$
—	—	—	—	CL	CL	Test with individual $\varphi s B_4, G, H, J, L$
CL	CL	CL	CL	CL	CL	Type A. Test with $\varphi A$
+++s	—	±s	±m	CL		Type B <sub>1</sub>
CL	—	—	—	CL		Type B <sub>2</sub>
+++s	++m	+++s	+++s	CL		Type B <sub>3</sub>
—	—	—	—	CL		Test with $\varphi s, B_1, B_2$ and $B_3$
—	—	—	—	CL		
—	—	—	—	CL		
—	—	—	—	CL		Type C. Test with $\varphi C$
—	S C P	—	—	CL		Types D <sub>1</sub> and D <sub>2</sub>
—	+++m	—	—	CL		Type D <sub>3</sub>
—	—	CL	—	CL		Types E <sub>1</sub> and E <sub>2</sub> . Test with $\varphi s E_1$ and $E_2$
—	—	—	CL	CL		Types F <sub>1</sub> and F <sub>2</sub> . Test with $\varphi s F_1$ and $F_2$

CL = Confluent lysis.  
 S.C.P. = Semiconfluent plaques.  
 + = Isolated plaques.  
 n = Normal size plaques.  
 s = Small plaques  
 m = Minute to microscopic plaques.

reduce the number of necessary tests to a minimum, by using initially only phage preparations homologous with the most frequent types. The frequency with which the various types have been encountered is indicated in the last column of Table II. The scheme for testing presented in Table III is offered as a suggestion until the frequency of types is known.

When the frequency of the types becomes apparent, the scheme may be suitably modified. If it should be found, for example, that type D is infrequent and type C or type J is common,  $\varphi C$  or  $\varphi J$  may be substituted for  $\varphi D_2$  in the first test. Rarity of imperfect V forms

or types B<sub>4</sub>, G, H and M might also suggest that the use of  $\varphi I$  and  $\varphi IV$  and the polyvalent phage preparation might be dispensed with in the first test, which would thus be reduced to the use of  $\varphi B_2$ ,  $\varphi E_2$ ,  $F_2$  and  $\varphi C$  or  $\varphi J$ .

#### Epidemiological Significance of Types and Subtypes of *B. Typhosus*

—As far as the main types of *B typhosus* are concerned, no definite evidence of change of type either *in vitro* under normal conditions of subculture, or on human transfer of infection, has been obtained as yet. In the case of the subtypes of types B, D, E and F, however, epidemiological evidence is not sufficiently extensive to justify conclu-

sions regarding their stability within the limits of the main type Helmer, Kerr, Dolman and Ranta<sup>10</sup> (1940) have reported the simultaneous isolation of subtypes F<sub>1</sub> and F<sub>2</sub> from a case, an observation which is of particular significance in this connection. However, although the subtypes may eventually prove to vary within the limits of the main type to which they belong, their differentiation at present provides almost the sole means of obtaining evidence of their stability and consequently their epidemiological significance.

Apart from the change from imperfect to typical V form which has been occasionally seen and does not actually constitute an example of type instability, only 2 unconfirmed observations on change of type under special conditions of culture have been observed. In these instances, type A was recovered from cultures of type B<sub>1</sub> and type C respectively, the latter after passage through an immunized mouse. The position of type A, which possesses the peculiarity of being fully sensitive to all type II phage preparations, remains obscure. However, the alterations in phage reactions produced by adding a small proportion of type A organisms to any of the types indicate that the dissociation of type A from any of the other types hardly can be overlooked. It may be said, therefore, that the unconfirmed observations on the appearance of type

A in a type B<sub>1</sub> and a type C culture does not invalidate the conclusion that the main types are stable.

In conclusion, it may be stated that the present classification of types is not regarded as final. Studies in progress would seem to indicate that it is unlikely that the present classification will have to be extended indefinitely by allocating new letters and numerals to new types and subtypes as they are encountered. Instead, there would seem to be definite prospect that further investigations will result in the development of supplementary methods which would permit the adoption of a simpler and less empirical scheme of classification.

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## BIOCHEMISTRY

*Edited by* VICTOR C. MYERS, A.M., Ph.D., Sc.D.

### BIOCHEMISTRY OF BLOOD

#### URIC ACID

*By* VICTOR C. MYERS, A.M., Ph.D., Sc.D.

Two recent observations have significantly advanced knowledge regard-

ing blood uric acid. Talbott and Coombs,<sup>1</sup> Jacobson<sup>2</sup> and their coworkers have shown that relatively higher and more uniform values for the uric acid of the blood may be obtained if

serum, rather than whole blood, is employed for the analysis. The use of serum collected under oil is recommended. Blauch and Koch<sup>3</sup> have introduced a very valuable new check method of uric acid estimation. They have been able to show with the aid of the enzyme, uricase, that the results obtained with the direct method on whole blood of normal subjects are about one-third too high, *i. e.*, too high by about 1.0 mg. They found the average value for 50 samples of human whole blood to be 2 mg. per 100 cc., with a range from 1.0 to 3.8 mg., while the direct method without the use of uricase gave an average of 3 mg. and a range from 1.8 to 4.6 mg.

Employing serum, separated under oil, Jacobson<sup>2</sup> found the fasting uric acid in 100 nongouty individuals on a mixed diet to range from 1.9 to 67 mg. per 100 cc., with a mean of 4.2 mg. In 97 individuals the serum uric acid was less than 60 mg. In 177 analyses on 21 cases of gout the serum uric acid ranged from 52 to 148 mg., 98 per cent of the values exceeding 6.0 mg., and 94 per cent 7.0 mg. Some evidence of correlation between the onset of an attack, the severity of the disease, and the level of serum uric acid was presented. In connection with a metabolic study of 24 cases of gout Talbott and Coombs<sup>1</sup> found that the serum uric acid values ranged from 5.7 to 14.2 mg. per 100 cc., the average minimum values being well over 7.0 mg. They interpreted the increased concentration of uric acid as due to increased formation rather than diminished excretion or destruction.

More recently Talbott<sup>4</sup> has made a study of the level of the serum uric acid in 136 relatives of 27 patients with gouty arthritis. The serum uric acid was normal in 102 of the group, the

average being 4.6 mg. per 100 cc. In the remaining 34 (83 per cent males) the serum uric acid content varied from 6.1 to 10.8 mg., with an average of 7.3 mg. per 100 cc. As a result of these findings Talbott concluded that an elevated serum urate, an essential component of the gouty diathesis, may be observed in symptom-free members of gouty families. The heredity in gout is also stressed by Hill<sup>5</sup> and is supported by the findings of Jacobson,<sup>2</sup> who noted elevated uric acid values in the son of each of 2 gouty individuals and in the brother of the third, they themselves being free from the symptoms of gout.

Price<sup>6</sup> has reported 5 cases of congestive heart-failure in which attacks of gout followed diuresis produced by salyrgan. This author feels that in view of these observations, the nature of the diuresis effected by salyrgan in the edematous subject assumes considerable interest, since the "critical" diuresis achieved by salyrgan closely parallels a "critical" diuresis preceding the ordinary attack of gout, the latter having also been pointed out by Talbott and Coombs.<sup>1</sup>

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## INORGANIC CONSTITUENTS OF THE BLOOD

By BENJAMIN KRAMER, A.M., M.D.

### Potassium

The factors which determine the concentration of potassium in blood plasma are but imperfectly understood. That the mechanism is a very efficient one is indicated by the constancy of the potassium concentration both during health and in most diseases. Nevertheless, it is now evident that at times this constancy may be disturbed either with or without the appearance of clinical phenomena.

In 1931, A. B. Hastings and E. L. Compere showed that the concentration of potassium in the blood of dogs increased after the removal of the adrenal glands. Before death, this often reached a value of 20 millimols per liter or about 62 mg per 100 cc of plasma, a value which has been found lethal for normal dogs following the injection of large amounts of potassium. One year later, R. F. Loeb reported an increase of serum potassium in patients with Addison's disease. The injection of adrenalin either in human beings or into dogs produces a transient elevation followed by a lowering of the serum and whole blood potassium level. When the adrenalin injections are repeated, a level of 70 mg per 100 cc of plasma or 23 m eq/liter may be reached. In some instances the initial rise following the adrenalin injection may be missed. The increase in total potassium is the result of an increase in red cell volume, while the increase in plasma potassium is probably due to migration of potassium from the tissue cells. Potassium, sugar and inorganic phosphorus of the blood plasma seem to be intimately related to the metabolism of carbohydrate in the muscles, as indicated by the fact that at times all 3 components may decrease in the blood simultaneously under the influence of insulin or adrenalin, while the ingestion of a large amount of sugar may be followed by a decrease of both serum potassium and inorganic phosphorus.

B. A. Houssay, A. D. Marenzi, and R. Gerschman, and also J. L. D'Silva, have shown that potassium is mobilized from the liver under the influence of adrenalin. R. F. Loeb, D. W. Atchley, and W. Parsons have confirmed the elevation of serum potassium in Addison's disease. This would occasionally occur with normal serum sodium

or fixed base and normal nonprotein nitrogen, but an elevation of serum potassium concentration is seen less often than is a reduction of plasma sodium or fixed base concentration. Fatalities may occur in patients with adrenal insufficiency even with minimal changes in plasma electrolytic concentration, an indication that these changes when present do not represent the basic chemical pathology of the disease.

Kramer, Tisdall and Howland have shown that in infantile tetany an increase in serum potassium level is present in more than 50 per cent of the cases. When tetany is produced in dogs either by the injection of a concentrated solution of potassium salts intrathecally or by the injection of a solution which robs the cerebrospinal fluid of its calcium or of its calcium ions there is a definite increase in the potassium content of the whole blood and of the plasma. The former is due to an increase in red cell volume, while the latter is caused by a migration of potassium from the tissue cells into the blood plasma. The increase in plasma potassium may vary between 20 and 40 per cent, being maximal when citrate solution is used to produce tetany. The change in the plasma potassium level parallels the intensity of the convulsions induced by the agents injected. Similarly, when asphyxia is produced by clamping the trachea of the animal, the plasma potassium increases about 30 per cent, while the whole blood potassium rises about 15 per cent.

Mullin, Dennis and Calvin<sup>1</sup> have shown, in confirmation of previous observations by Mullin, Leeds and Hastings, that a relative or absolute rise in the potassium content of the media bathing the central nervous system causes a definite increase in activity

and a lowering of the threshold of neuromuscular irritability. Perhaps, as M. Vogt and G. L. Brown and W. Feldberg suggest, this may be due to the action of potassium in facilitating synaptic conduction. So far no instance of clinical tetany due to increased serum potassium alone has been described.

One of the most striking clinical conditions associated with serum potassium deficit is illustrated by the disease known as periodic family paralysis. This is a familial and hereditary disease which is compatible with long life but which is characterized by periodic attacks of weakness of the extremities followed by complete paralysis. This may involve either the upper or lower extremities alone or may involve all the extremities. Cases in which the muscles of the trunk are also affected have been described. The seizures may come on at any time of the day or night but most frequently occur between 3 and 4 A. M. The patient awakens to find himself either unable to raise his head from the bed or to move one or more extremities. The paralysis lasts from a few minutes to a few hours, when muscle power gradually returns and finally is fully restored without residua.

In 1902, J. K. Mitchell, S. Flexner and D. L. Edsall thought that the administration of potassium citrate exerted a beneficial effect on the seizures and in 1938, McCann found that the descendants of Mitchell's patients were still relying on the drug for relief.

T. Shumusak and K. Yoshimura showed that the injection of adrenalin or insulin or the ingestion of large amounts of glucose will precipitate an attack. All these factors are now known to produce a lowering of serum potassium concentration. Gammon<sup>8</sup> and

Gammon, Austin, Blithe and Reid<sup>9</sup> accomplished the same thing by water diuresis. Bremmond and Daniels, in 1934 recorded a value of 13.38 mg. potassium per 100 cc. of serum in a patient suffering from *periodic family paralysis* during a mild spontaneous attack compared with 17.87 mg. in 100 cc. during a free interval. They did not appreciate the significance of their observations. The development of quantitative micromethods for the determination of potassium in serum made possible a study of the quantitative relation between the serum potassium and the seizures. It is now known that measures which provoke a seizure all reduce the serum potassium concentration and that this reduction occurs regularly with each attack. The existence of hypopotassemia has been repeatedly confirmed and the mechanism of the reduction has been elucidated. The subject has been studied both in this country and abroad and the results have been remarkably uniform. Thus, it has been established that either immediately preceding or during the seizure the serum potassium level drops. Although there is no exact level at which symptoms appear, they usually do not become manifest until the potassium level has dropped to 12 mg. per 100 cc. or less. In an effort to find the mechanism of this decrease it has been shown, and there is a striking unanimity of opinion among observers, that the seizures are preceded by a decrease in the urinary excretion of potassium. This persists during the attack but following the attack, *i. e.*, after recovery is complete, there is a potassium diuresis as if the extra potassium were no longer needed. The administration of large doses of potassium citrate or chloride by mouth will prevent an attack if given shortly before or promptly relieve the

symptoms even when they are fully developed. This treatment with potassium salts is followed by a retention of potassium in the tissues. Not all of this, however, comes from ingested potassium. The blood plasma and extracellular fluid may give up more than 50 per cent of their potassium to the cells. The potassium deficiency in the serum is, however, not the cause of the symptoms since in normal individuals the same degree of serum potassium deficit may be produced without symptoms and potassium salts injected slowly intravenously may relieve the seizure without correcting the hypopotassemia.

*Periodic family paralysis* seems to be due to a transient disturbance of potassium metabolism in the neuromuscular system. This creates an extra demand for potassium ions. As long as the exogenous supply is adequate nothing happens just as when calcium supply is adequate in tetany. When this supply becomes inadequate, however, as during the postabsorptive period, *i. e.*, in the early morning hours, potassium is withdrawn from extracellular fluid and from the blood plasma. When this no longer suffices, muscular weakness supervenes, followed by complete paralysis of the neuromuscular apparatus. At this stage serum potassium has reached a level between 6 and 12 mg. per 100 cc. of plasma. The muscles and nerves no longer respond to electrical stimuli. The reason for this may be ascribed to the intimate relationship between potassium concentration and synaptic conduction, an excess of potassium ion facilitating this process, while a decrease has a retarding effect. When potassium salts are administered they pass rapidly into the tissues to correct the deficiency. If the supply is adequate, the blood serum

potassium level is restored. Still later, when the metabolic defect has been corrected and the extra potassium is no longer needed, it is excreted into the urine.

The relation of plasma potassium concentration to *status epilepticus* has been studied by I. McQuarrie, R. Engel and M. Ziegler, who found the serum potassium level increased during the convulsions. They found no constant level, however, at which convulsions were certain to occur or to subside. In 72.2 per cent of cases the potassium level was normal while high values varying from 35.8 to 54 mg. were observed at times during status epilepticus.

### Calcium

The cause of the mild hypocalcemia which occurs during the latter months of pregnancy has been studied by Bodansky and Duff.<sup>10</sup> During the second trimester of pregnancy the average serum calcium was found to be 9.8 mg. in 100 cc. of serum in 300 pregnant women studied. At the ninth lunar month this value dropped to 9.49 and at term was 9.50. In many instances there was a tendency to the development of a hypocalcemia of less than 9 mg. in 100 cc. of serum. This tendency increased up to the ninth lunar month, varying from 6 per cent of the patients studied in the second trimester of pregnancy to 24 per cent in the ninth lunar month of pregnancy.

The authors found no evidence of hypoparathyroidism to explain this hypocalcemia. Neither could it be explained as due to increase in plasma water, *i. e.*, to a dilution effect, nor to a reduction in serum protein, *i. e.*, referable to a decrease of protein bound calcium. The serum calcium concentration in the fetus was found regularly to be



higher than that in the mother's plasma, while the amount of calcium in the fetal placenta was greater than that in the maternal. The authors attributed more severe degrees of hypocalcemia in pregnant women either to a deficiency of calcium in the diet or to lack of vitamin D or both.

### Magnesium

Hirschfelder and Haury<sup>11</sup> have extended their work on the relation of serum magnesium level to essential *epilepsy*. They have confirmed their previous finding of a low serum magnesium in some patients either before or during epileptic seizures. This is, however, not a regular finding, nor does it correlate with the clinical symptoms, since some patients in status epilepticus have been found to have a normal serum magnesium concentration, while others who were treated with magnesium salts have responded with an elevation of serum magnesium concentration up to 7 mg. per 100 cc. plasma without any effect upon the number or severity of the seizures. In their more recent work the authors stress the importance of the molar ratio of potassium to magnesium, especially the ratio of potassium to ultrafiltrable magnesium. They state that all these abnormalities are most intense in the convulsive form and are less frequent and less intense before and after the convulsions and tend to return to normal between seizures. In the case of high potassium value the increased muscle metabolism during status epilepticus may result in the liberation of excess potassium from the muscles and perhaps from the other tissues, resulting in a temporary elevation of serum potassium.

Soffer, Dantes, Grossman, Sabotka and Jacobs<sup>12</sup> have reported an increase of bound magnesium in *hyperthyroid-*

*ism*. This work has been carefully controlled by a study of the total and ultrafiltrable magnesium of the plasma of normal individuals and of patients with neurocirculatory asthenia, progressive muscular dystrophy and myasthenia gravis.

In normal individuals the total magnesium showed an average value of 2.52 mg. in 100 cc. of serum with a variation of 2.12 to 2.60 including one value of 4.30. The magnesium in the ultrafiltrate averaged 2.15, varying from 1.72 to 2.47, *i. e.*, the percentage of bound magnesium varied from 3.1 to 22.1 per cent which in absolute figures represents a variation from 0.08 to 0.4 mg. in 100 cc. Similar findings were obtained in neurocirculatory asthenia, myasthenia gravis and progressive muscular dystrophy. In patients with hyperthyroidism, however, in whom the basal metabolism was increased from 30 per cent to 106 per cent above the normal, the total magnesium averaged 2.44 mg. (normal 2.52), varying from 1.85 to 2.96, while the magnesium concentration in the filtrate averaged 1.58 mg. varying from 0.86 to 2.08. This represents a bound magnesium averaging 36 per cent of the total and varying from 21.5 to 61.6 per cent. After the administration of Lugol's solution the amount of bound magnesium decreased and a further decrease was observed after thyroidectomy. In an effort to elucidate the causes of this increase in magnesium associated with hyperthyroidism, 50-200 mg. of thyroglobulin were injected intravenously in 1 dose into 5 dogs and the total and ultrafiltrable magnesium was determined after 15 minutes, 1 hour, 5 hours and 24 hours. In each instance the increase in bound magnesium varied between 30-100 per cent above the control level. Thyroxin and horse serum were

without effect. In patients with myxedema the bound magnesium decreased almost to zero. The authors have observed the same to obtain after thyroidectomy in animals (Personal communication). In explaining their results the authors quote Elsie Watchorn and R. A. McCance who state that bound magnesium may be in combination either with protein or with serum phosphate, forming with the latter a colloidal magnesium phosphate complex similar to the colloidal calcium complex described by McLean and Hastings. This observation is important not only in indicating a specific disturbance in the equilibrium between electrolytes and certain nonelectrolytes in the blood of patients with hyperthyroidism, but as furnishing an additional diagnostic criterion of hyperthyroidism as well as an objective and possibly quantitative measure of the effects of medical and operative treatment. The technical difficulties in the quantitative estimation of such minute quantities of magnesium suggest caution in accepting these results until confirmed by other workers.

Unfortunately, inorganic phosphate determinations are not reported. It is conceivable that in hyperthyroidism where there is an increased mobilization of phosphate from bone an increase in serum phosphate may increase the amount of colloidal magnesium phosphate complex which may then fail to pass through the collodion filter, giving a higher value for bound magnesium. That such a complex may affect the ultrafiltrability of calcium has been shown by Grollman, and that magnesium itself may form a colloid phosphate complex which may affect the availability of phosphate for *in vitro* calcification has been shown by Shelling, Kramer and Orent.\*

### Hypochloremia

The depletion of serum chloride and of fixed base in Addison's disease is now well known as is the hypochloremia of pneumonia, nephritis and congestive heart-failure. In *pneumonia* the administration of large amounts of sodium chloride is followed by retention of the added salt and a restoration of chloride and sodium to the normal level.

Winkler and Crankshaw<sup>13</sup> report a group of patients suffering with a variety of clinical conditions including *pulmonary tuberculosis, carcinoma of the lung, and cardiac disease*. All of these showed a hypochloremia varying from 86-96 m.eq. of chloride per liter (normal 100 m.eq./l). The ingestion of added sodium chloride raised this value to about 95 m.eq. per liter but never to an entirely normal level. This increased intake of sodium chloride was accompanied by an increased urinary excretion of sodium chloride. Hypochloremia was maximal when sodium chloride intake was reduced so that measurable amounts of chloride continued to appear in the urine when under normal conditions only traces of chloride would have been detectable in the urine. Post-mortem examination of the kidneys and adrenals revealed nothing abnormal. Since none of these patients recovered, it is not known whether this condition is reversible. It is apparently not an expression of an adrenal insufficiency, since not only was there no disease of the adrenals but the condition failed to respond to adrenal cortical extract. It is suggested, therefore, that this is a functional disturbance in which there is a low renal threshold for chloride with little tendency toward retention of added salt.

\* Soffer states that subsequent observations have shown no increase in inorganic phosphorus of the serum in hyperthyroidism.

## IODINE

By J F McCLENDON, M S , Ph D

Micrograms of iodine per kilogram of blood have been reported for human 20 to 320, dog 56, goat 90 to 110, guinea-pig 7 to 350, ox 60 to 200, rabbit 30 to 190, sheep 24<sup>14</sup> This great variability is due partly to errors in analysis and partly to variations in the intake and elimination of iodine and only to a small extent to storage of iodine in the thyroid gland In a series of *gout* patients the blood iodine varied inversely with the basal metabolic

rate, showing preponderant influence of elimination<sup>15</sup> Perkin and Hurxthal<sup>16</sup> found no correlation of the organic blood iodine with the basal metabolism rate, but found low values in *myxedema* and high values in untreated *exophthalmic gout* McClendon and Foster<sup>17</sup> described a method of determining thyroid hormone iodine in blood, and McClendon, Foster and Kirkland<sup>18</sup> found a correlation coefficient of  $+0.627$  between these values and the basal metabolism rate Curtis<sup>14</sup> and Perkin and Lahey<sup>19</sup> have made extensive studies in blood iodine

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## CHEMISTRY OF MUSCLE CONTRACTION

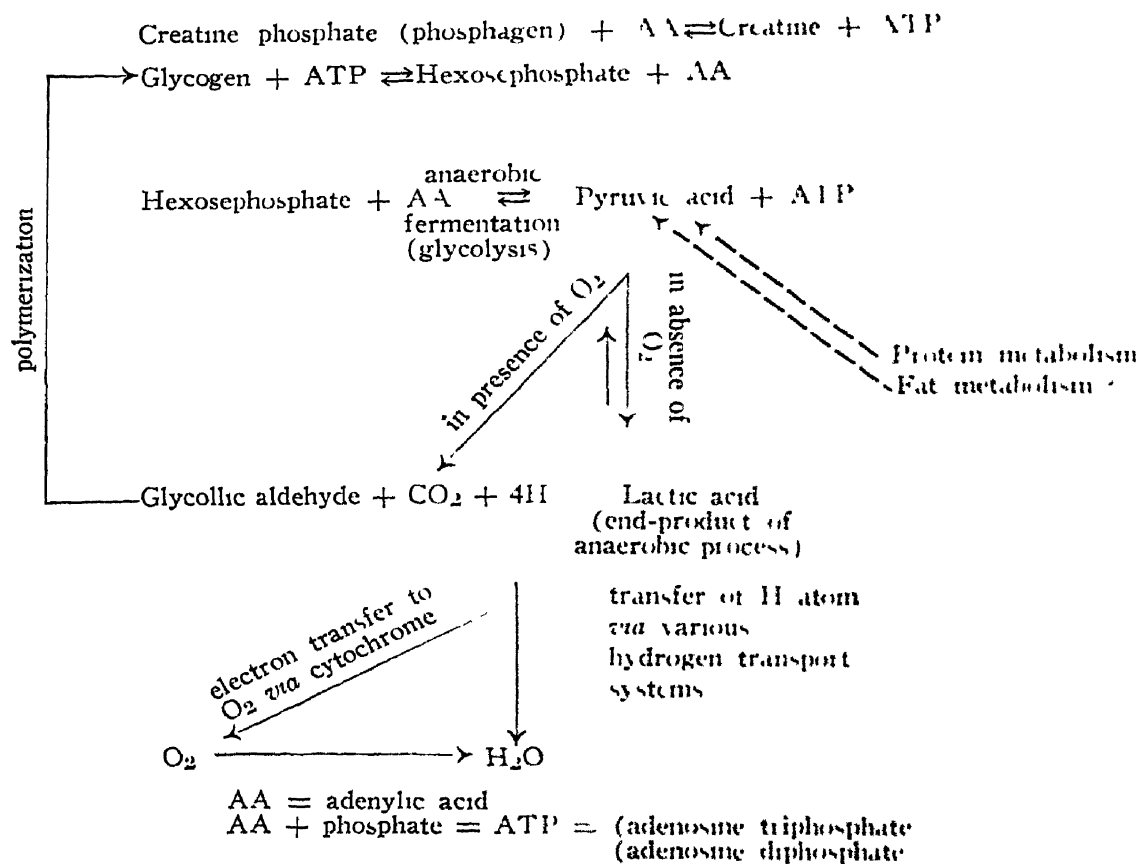
By A S MINOT, A B , Ph D

Experimental studies carried on in the past 10 or 15 years have brought about radical changes in the concept of the chemistry involved in the derivation of energy through the utilization of foodstuffs by a muscle It is now realized that the changes in creatine phosphate and other phosphorous compounds which were observed to occur during different phases of the contractile process play an intimate and vital rôle in the utilization of carbohydrate During recent years a great deal also has been learned in regard to the intermediate steps involved in the oxidative processes in muscle.

The schematic representation on the following page illustrates the main features of the system by which muscle derives from carbohydrate degradation the chemical energy which is converted into mechanical work

Shortening of a muscle fiber is accompanied by the breakdown of creatine phosphate This reaction yields a certain amount of energy Adenylic acid acts as an agent for the transfer

of phosphate in the reversible breakdown of creatine phosphate and in the cyclic reversible fermentative system which degrades glycogen by way of hexosephosphate to pyruvic acid (It is probable that the utilization paths of protein and fat in muscle also lead to pyruvate) Thus far the processes involved are anaerobic, *i e*, they require no oxygen The older erroneous idea was that anaerobic glycolysis always goes on to the formation of lactic acid Now it is known that only when the oxygen supply is deficient is the pyruvic acid reduced to lactic acid by hydrogen transfer from one of the components of the fermentation process Ordinarily, with a normal supply of oxygen, the pyruvate undergoes aerobic oxidation through a process the details of which are not as yet entirely clear. For this step the diagram merely outlines a working hypothesis which integrates with most of the experimental observations Decarboxylation and oxidation (transfer of H atoms) yields a biose



(glycolic aldehyde) which polymerizes to rebuild glycogen. The CO<sub>2</sub> is derived from decarboxylation of pyruvic acid or a related derivative. The hydrogen atoms are transported by reversible oxido-reduction systems through a series of reactions finally leading to the formation of water by combination with oxygen. The chemical energy released in these reactions is presumably used to reconstruct creatine phosphate and for conversion into mechanical energy. The energy released in the anaerobic process is small, that of aerobic oxidation is large. The former,

therefore, is a wasteful process which rapidly depletes the carbohydrate stores and explains the small capacity for work of a muscle contracting in the absence of oxygen. Vitamins are intimately concerned with muscle metabolism. B<sub>2</sub> (nicotinic acid) is a component of co-enzymes involved in both fermentation and aerobic oxidation. B<sub>1</sub> (thiamin) is a component of cocarboxylase which catalyzes the decarboxylation of pyruvic acid or its derivative. Any detailed discussion of the details of the intermediate reactions involved are outside the scope of this summary.

## CHEMICAL EXAMINATION OF DUODENAL CONTENTS

By VICTOR C. MYERS, A.M., Ph.D., Sc.D., and ALFRED H. FREE, M.S., Ph.D.

During the past 3 years there have appeared several contributions to the chemical examination of duodenal contents as aid to the diagnosis of gastro-

intestinal disorders. In general, these have been directed either towards the examination of enzyme activities or the consideration of biliary constituents.

McCaughan, Sinner, and Sullivan<sup>20</sup> studied the *external secretory function of the pancreas* in a patient who developed a pancreatic fistula. The average volume of the pancreatic secretion was estimated to be 600 cc. per day. A rise in the secretory rate followed the administration of secretin, a mixed meal, water, hydrochloric acid, beef broth, dextrose, olive oil, peptone, coffee, mecholyl and physostigmine. A fall in the secretory rate occurred after the administration of sodium bicarbonate, bile salts, magnesium sulfate, atropine, epinephrine and histamine. Myers, Free and Beams<sup>21</sup> have reported the development of improved chemical techniques for the measurement of enzyme activities in duodenal contents and have devised a system for the simplified expression of the results of enzyme analyses. By these methods values in certain pathological cases are clearly differentiated from figures obtained in normal subjects. Very low values were observed in proven cases of pancreatitis, while somewhat subnormal figures were obtained in a variety of gastrointestinal disorders in which some affliction of the pancreas might be expected.

Lagerlöf<sup>22</sup> reviewed the technic and summarized the findings of the group of Swedish investigators who first developed the successful technic of using *purified secretin* as a stimulant for pancreatic secretion. When this stimulant is used the bicarbonate excretion by the pancreas parallels the volume of excretion whereas the enzyme concentration is inversely proportional to the volume. This group of investigators believe that the secretion of amylase by the pancreas is the most sensitive indicator of pancreatic function. In a group of 35 cases of pancreatic disease a marked decrease of amylase was noted in 22 instances with suggested decrease

in 6 of the remaining cases. Berger and Schnetz<sup>23</sup> found decreased amylase and trypsin secretion by the pancreas in 7 patients in whom the pancreatic disease was established either by autopsy or biopsy material. The internal pancreatic function was also studied in these cases and in the majority there was a decreased insulin production although in 2 of the cases the internal secretory activity was augmented. This series included 2 cases of lipomatosis of the pancreas, 2 of pancreatic edema, 2 of pancreatic necrosis, and 1 case of carcinoma of the pancreas.

Studies of *enzyme activities of duodenal contents* have been reported by Comfort, Parker and Osterberg<sup>24</sup> in a series of patients and normal individuals. The normal range of enzyme concentration observed was quite large. According to these investigators, the concentration of amylase, trypsin, and lipase was practically normal in the presence of *intrahepatic jaundice* caused by cirrhosis or hepatitis, *obstructive jaundice* caused by stone in or a stricture of the common bile-duct, *biliary disease* which is associated with or a residuum of acute edematous pancreatitis, and *nontropical sprue*. A marked contraction of the range of enzyme concentrations was noted in samples of duodenal contents obtained from patients with *carcinoma of the head of the pancreas*, *carcinoma of the ampulla of Vater*, and *chronic atrophic pancreatitis with steatorrhea*. In cases of chronic pancreatitis not associated with steatorrhea there was no remarkable deviation from the normal range.

Comfort and Osterberg<sup>25</sup> have quite recently studied the relative *effects of secretin and mecholyl chloride on pancreatic enzyme secretion* in human subjects. Secretin, in accordance with the

results of Agren and his associates, produced a large volume of duodenal contents, increased the pH values and effected a prolonged reduction in the concentration of enzymes. Mecholyl chloride, on the other hand, increased the volume of duodenal contents only slightly, did not appreciably affect the pH values and produced a prolonged increase in the concentration of enzymes. In the case of secretin there was a washing out effect on preformed enzymes, whereas the mecholyl chloride seemed to stimulate the formation of enzymes by the pancreatic cells. These investigators suggest that enzyme concentration is perhaps a more valuable index than total enzyme output as a measure of pancreatic function. The writers are in accord with this view, particularly since no technic is at present available that insures complete collection of duodenal contents.

Meyer, Spier and Neuwelt<sup>26</sup> have measured the *fasting concentration of enzymes of duodenal contents* as well as *pepsin of gastric juice* and *ptyalin of saliva* in various age groups between 12 and 96 years. A slightly subnormal value for pancreatic amylase and a somewhat decreased concentration of proteinase (trypsin) was observed in the older subjects. There was relatively little change in lipase in the older group. These authors suggest that their findings may be important in the dietary management of old persons. Most investigators have found that a more uniform response of enzyme secretion by the pancreas is obtained after employing some stimulant such as olive oil, cream, or secretin. It would seem necessary, therefore, to study enzyme concentrations after stimulation as well as in the fasting state before any generalities could be arrived at regarding

the secretion of the pancreas by various age groups

Diamond, Siegel, Gall and Karlen<sup>27</sup> have employed the secretin test of Lagerlof and Agren and were able to offer confirmation to their findings. The effect of secretin on the biliary tract was also confirmed by Diamond and his associates<sup>28</sup>. In a later publication<sup>29</sup> the results of studies on 24 normal and 80 pathological cases are summarized. Various degrees of disturbed pancreatic function were noted in *cholelithiasis*, *lues*, *liver cirrhosis*, *chronic alcoholism*, *acute yellow atrophy* and in the graver forms of *toxic hepatitis*. These investigators<sup>30</sup> have also reported studies with 14 cases of *steatorrhea*. In all of these cases the symptoms were similar but varied in severity, and in general the patients appeared to have sprue. In 10 of the 14 cases there was a decreased lipase concentration in the duodenal contents following stimulation with secretin. Five of the cases showed a diminished trypsin output, 4 a diminished volume, and 2 a diminished bicarbonate concentration. By repeating the studies in various phases of the disease a gradual improvement in the apparent pancreatic function was observed to occur with clinical improvement of the patients, which would lead to the conclusion that the pancreatic lesion was of a reversible nature.

Bollman and Mann have shown that *bile acids* are produced and destroyed in and only by the liver. Accurate simple chemical methods for the determination of bile acids are not available at the present time. Doubilet has published a detailed method for the differential quantitative analysis of bile acids in bile and duodenal drainage material but has cautioned regarding the

difficulties of the technic. By this method it is possible to analyze bile for taurocholic acid, glycocholic acid, total conjugated bile acids, cholic acid, desoxycholic acid, total bile acids, and free bile acids.

Gray, McGowan, Nettrour and Bollman<sup>31</sup> conducted a clinical study in 50 cases in which drainage of the common bile-duct was established by means of a *T-tube*. The condition of the liver was estimated from the history, from the results of recognized tests of hepatic function, and from the gross appearance of the liver at operation. The degree of hepatic damage thus determined was correlated with frequent determinations of the concentration of bile acids in the bile. Low concentrations occurred in every case in which there was other evidence of hepatic damage and the degree of damage was proportional to the extent of decrease in the bile acids.

Doubilet and Colp found that after the relief of obstruction uncomplicated by infection the cholic acid of hepatic bile constituted about 50 per cent of the total bile acid content. In the presence of inflammation of the bile-ducts, cholic acid formed about one-sixth of the total bile acid content, indicating that cholic acid is probably absorbed by the inflamed ducts. In cases of acute hepatitis cholic acid formed about 80 per cent of the total bile acid content.

Morrison and Swalm<sup>32</sup> have suggested that the simple indirect estimation of surface tension by a stalagmometer affords an accurate measure of the bile salt content of either duodenal contents or urine. These men state: "The bile salt concentration in the bile from surgical and nonsurgical drainage is the most sensitive, accurate and practical

liver function test at present available in humans, in the experience of the authors."

Royer<sup>33</sup> has studied the *bilirubin* and *urobilin* content of A bile and B bile obtained by duodenal drainage. In normal individuals there is a higher concentration of bilirubin and urobilin in the B bile than in the A bile but the increase of urobilin concentration is usually much less than that of bilirubin, which indicates that only a small amount of bilirubin is absorbed by the gall-bladder while a relatively large amount of urobilin may be reabsorbed. In certain cases of cholecystitis indication of urobilin production in the gall-bladder was observed. This was apparently due to bacterial action which converts bilirubin to urobilin. It was suggested that the demonstration of urobilin increase in B bile at the expense of bilirubin is a valuable aid in making a differential diagnosis of inflammation of the gall-bladder. Such changes, however, were noted in only 41.4 per cent of Royer's series of patients with cholecystitis.

Rigney, Mortensen and Miller<sup>34</sup> compared the value, in the diagnosis of gall-bladder disease, of cholecystography and examination of duodenal contents for *cholesterol crystals*. In a series of 137 operated cases approximately the same accuracy was noted with either technic and the authors recommend that both tests should be routinely employed in suspected cases of chronic gall-bladder disease. Doran, Forster and Spier<sup>35</sup> in 64 operated cases found that non-surgical drainage compared favorably with x-ray diagnosis of biliary tract pathology. The presence of crystals in the biliary drainage was not pathognomonic of stones but did give evidence of pathology in the biliary tract.

## CHEMISTRY OF CARBOHYDRATES OF FOODS AND BODY TISSUES

By JOSEPH H. ROE, Ph D

### Availability of Carbohydrates —

The carbohydrates known to be available to man are d-glucose, d-fructose, d-galactose, and the polymers of these monosaccharides (sucrose, maltose, lactose, starch, dextrans, glycogen) which are hydrolyzed by the enzymes of the alimentary tract. Inulin, agar, and cellulose are not digestible and hence not available to man. d-Mannose will alleviate hypoglycemic convulsions in animals produced by insulin or hepatectomy, and forms glycogen in the rat,<sup>36</sup> hence d-mannose is probably utilizable by man.

Arabinose and xylose do not relieve insulin convulsions. d-Xylose is not metabolized by the rat. In a xylose clearance test, the normal subject, after ingesting 50 grams of xylose, concentrates this sugar in the urine to 2.5 per cent and excretes 25 per cent in the urine in 24 hours. It thus appears that xylose is not available to man. d-Xylulose (d-ketoxylene) forms glycogen in the rat. l-Xylulose, the sugar occurring in pentosuria, does not form liver glycogen in rats, but gives rise to "extra" glucose in the urine of the depancreatized dog.<sup>37</sup>

d-Mannoheptulose (d-mannoketose), a 7-carbon sugar occurring in

the avocado pear, is metabolized by the rabbit, but not by the rat. When 137 to 214 grams of avocados were ingested by normal human subjects, mannoheptulose was excreted in the urine in quantities sufficient to give positive Benedict's tests.<sup>38</sup> The latter studies did not show whether or not d-mannoheptulose is available to man, but they indicate another source of confusion in the diagnosis of melurias.

Availability of sugars is related to structure. The d-sugar is the only form known to be utilized by animals (the metabolic fate of l-xylulose is uncertain). l-Glucose is not fermented by brewer's yeast and is not metabolized by rat tissues, *B. coli communis* and *B. Aerogenes*.<sup>39</sup>

**Specificity of Blood Sugar Methods**—The early blood sugar methods developed by Folin and Wu, Lewis and Benedict, Shaffer and Hartman, and others, gave values that averaged 20 to 25 mg. per cent higher than the true sugar content. The use of yeast as a reagent to ferment the blood glucose enabled investigators to show the amount of nonsugar reducing substances in deproteinized blood filtrates. The following table indicates the amount of nonsugar reducing substances in blood by different blood sugar methods:

Method	Deproteinizing Agent	Authors of Data	Average Amount of Nonfermentable Reducing Substance mg./100 cc. as Glucose
Folin-Wu	Tungstic acid	Folin and Svedberg	29
Folin-Wu	Tungstomolybdic acid	S. R. Benedict	22
Shaffer-Hartman	Tungstic acid	Somogyi and Kramer	21
Folin	Tungstic acid	Folin and Svedberg	9
Benedict, 1931	Tungstomolybdic acid	S. R. Benedict	7
Somogyi	Zinc	S. R. Benedict	5



Folin and Benedict made their methods more specific by improving their copper reagents, making the latter less sensitive to reducing nonsugars. Somogyi made the important advance of using zinc and copper or iron as deproteinizing agents, the latter precipitating most of the nonsugar reducing substances along with the proteins.

The Folin-Wu method gives blood sugar values that average 20 mg. per cent higher than the true sugar concentration. The average blood sugar values obtained by the Folin (1926) and the Benedict (1931) procedures are greater than the true sugar contents by 9 and 7 mg. per cent, respectively. The Folin micro method gives values that average 6 mg. per cent lower

than those found by the Folin-Wu method. The most specific results are obtained by using a reliable reduction procedure upon filtrates prepared by the zinc or copper deproteinizing techniques of Somogyi (5 mg. per cent higher than true sugar values).

The less specific blood sugar methods are satisfactory for clinical use, except in hypoglycemic conditions, where a method giving true sugar values is desirable.

Matthews, Magath and Berkson<sup>40</sup> found the fasting blood sugar of 117 normal subjects by the Folin-Wu method ranges from 63 to 110 mg. per 100 cc. The normal blood sugar by specific methods ranges from 60 to 100 mg. per 100 cc.

## GASTRIC ANALYSIS

By DANIEL N. SILVERMAN, M.D., and ROBERT A. KATZ, M.D.

Notable recent contributions to analysis of stomach contents have been made by some workers who have all stressed the purely physiological and biological aspect of gastric function.

The secretagogue meal of Wilhelmj,<sup>41</sup> consisting of Liebig's extract and definite proportions of phenol red, sodium hydroxide, and sodium carbonate, was introduced to enable the clinician to make an accurate estimation of the volume of acid produced in the stomach, the time of its evolution, and finally the rate of its neutralization by nonacid secretion. This meal has the ability of causing the stomach to secrete hydrochloric acid promptly. There is nothing in the meal to bind with the acid, as is true when carbohydrate is administered. This method permits one to evaluate the amount of nonacid secretion produced by the stomach in comparison with material regurgitated from

the duodenum. Careful standardization and titration is required and the latter is best done where adequate laboratory facilities are available.<sup>42</sup> The analysis consists of (1) titration of the samples removed from the stomach and also of the test meal; (2) determination of the percentage of phenol red removed from the stomach.

The *acid reduction* or the *neutralization test*, as reported by Apperly and Phillips, has been used with noteworthy success in investigating the acid regulating mechanism in *duodenal ulcer*, *pyloric obstruction and spasm*, and finally in determining the success or otherwise of surgical treatment of *peptic ulcer*.

**Technic**—From 250 to 300 cc. of 0.4 to 0.5 per cent hydrochloric acid solution are introduced into the fasting stomach, through an indwelling nasal tube, after its contents have been re-

moved by aspiration. Withdrawal of samples are made every 15 minutes after thorough mixing is effected. Titration for free and total acidity is carried on as usual.

In the normal individual the *total acidity* falls from a value of 120 to 130 at the beginning to a low of 40 after an hour or so. In cases of duodenal ulcer the total acidity falls very slowly and is frequently within a few degrees of the initial reading after an hour, finally dropping to 60 to 70 after 3 to 4 hours. With this test a guess may be hazarded as to the degree of muscular in-co-ordination that is responsible for the retardation of acid reduction in the particular case studied.

The *double histamine test* has been advanced by Rivers, Osterberg and Vanzant as a method of studying *secretory function of the stomach*. They inject subcutaneously 0.1 mg. of histamine per 10 kg. of body weight. Aspiration is performed on a fasting stomach *via* indwelling tube in 6 periods of 10 minutes each. At the end of an hour the first dose is injected again. A curve is constructed after titration is effected. These workers have concluded that this test is useful in estimating the maximum potentiality of acid and pepsin secretory cells. An impression may be obtained of the time and rate of secretory activity.

The estimation of *pH values of gastric juice* has been made at the bedside by Silverman and Katz. They determined the optimum dosage of a magnesium trisilicate preparation<sup>43</sup> useful in the treatment of *peptic ulcer*.

A nasal tube was left in place and repeated hourly aspirations were made of fasting contents, food alone, and graduated doses of the drug studied. By this simple method they were able to adjust the proper dose to the indi-

vidual studied and were able to attain pH values of 2.4 and above with little trouble.

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## CLINICAL PATHOLOGY

By ROBERT A. KILDUFFE, A.M., M.D.

### HORMONE PREGNANCY TESTS

With the advent of the Aschheim-Zondek and, later, the Friedman test for pregnancy, the biologic diagnosis of this condition became established on a firm foundation. As is now rather well known, however, even these procedures have their limitations and are not to be regarded as under all circumstances infallible. For the hormonal tests for pregnancy depend, not upon the fact of pregnancy itself, but upon the fact that in this condition the urinary excretion of hormones reaches a degree rarely paralleled in other conditions. That appreciation of this is essential for the proper evaluation of these procedures is self-evident and it is of great interest to note the studies concerned.

McCullagh and Cuyler<sup>1</sup> have recently reported upon 2134 cases in which, in the absence of pregnancy or any evidence of the presence of chorionic tissue, positive Friedman tests occurred in 241 instances.

These reactions are not to be taken as comparable to the so-called "false positive" reactions which have been reported

where the test is done solely in connection with the diagnosis of pregnancy. In this series all the tests were conducted, not in connection with the suspicion of pregnancy, but in the presence of some endocrine abnormality and are thus of interest as showing the variety of conditions under which positive Friedman reactions may be encountered.

The technic used in these investigations was as follows:

Adult female rabbits which have been isolated for 3 weeks are used. Animals which have proved normal activity of their ovaries by bearing litters are preferred to virgins. Where a question of pregnancy in the animal is raised, the abdomen is opened and examined prior to the test and sufficient time allowed for complete recovery from the operation.

Concentrated morning specimens of urine are used. The patient is instructed to restrict the fluid intake after 4 P. M. to 1 glass of water at the evening meal and none thereafter until the rising specimen of urine is collected which is used for the test.

Four cubic centimeters of urine are injected into the ear vein of the rabbit on each of 3 occasions daily for 2 successive days and the abdomen is opened under ether anesthesia on the morning of the third day. The following findings are considered to constitute a positive reaction: (1) Freshly ruptured graafian follicles, (2) hemorrhagic follicles, or (3) fresh

corpora lutea. The degree of response is recorded as 1 to 4 plus on a basis of 4 in any one of the types of responses mentioned.

The cases showing positive Friedman reactions may be placed in 5 main groups:

*Group 1*—Those conditions associated with disorders peculiar to women—117 cases.

*Group 2*—Conditions associated with or possibly due to testicular deficiency or testicular tumor—23 cases.

*Group 3*—Endocrine disorders not sex specific—64 cases.

*Group 4*—Disorders of the nervous system and conditions in which nervous stimulation of the pituitary is suggested as a possible mechanism for excess gonadotropic hormone production—26 cases.

*Group 5*—Miscellaneous conditions not clearly endocrine in nature—11 cases.

When analyzed, the positive reactions in certain groups were thus divided:

#### DISEASES OF WOMEN

*Menopause*—Of 151 cases with menopausal symptoms positive reactions occurred in 51 or 32 per cent. Where active menopausal symptoms were the chief clinical picture, the reactions varied as shown:

Ripe follicles only.....	6
Fresh corpora lutea only.....	9
Ripe follicles and fresh corpora lutea but no hemorrhagic follicles.....	4
Hemorrhagic follicles alone or with other findings.....	32

Thus, in 63 per cent of these cases, the reaction was identical with that seen in pregnancy.

*Ovarian Deficiency Under 37 Years of Age*—In 430 cases (16 to 37 years old) positive reactions were encountered in 46 or 11 per cent, the intensity of the reactions varying.

Condition	No. of Cases	No. Positive Reactions
Castration.....	14	5
Severe prepubertal hypogonadism.....	10	2
Suspected testicular functional deficiency.....	45	7
Prostatic hypertrophy.....	34	7
Cryptorchidism.....	2	2

Positive reactions were also seen once in orchitis, once in aspermia and in 3 cases of impotence not associated with low androgen excretion. Weakly positive reactions were encountered in testicular tumors without chorionic tissue, a reticulum cell sarcoma, and 1 case of lymphangioma.

#### ENDOCRINE DISORDERS NOT SEX SPECIFIC

*Pituitary Tumors and Organic Lesions in the Hypothalamus*—Local lesions of the pituitary gland or adjacent region gave 12 positive reactions. In 31 cases of pituitary tumor verified by operation, indisputable clinical evidence, or autopsy there were 10 positive reactions.

#### CASES DIAGNOSED DYS-PITUITARISM ON CLINICAL GROUNDS

Condition	No. Cases
Pituitary dwarfism (and testicular deficiency).....	3
Pröhlisch syndrome.....	15
Hyperthyroidism.....	3
Diabetes mellitus.....	3
Adrenal cortical hyperfunction.....	21

*Disorders of Adrenal Cortex*—Positive reactions were seen in 12 cases in this group.

*Miscellaneous Conditions*—Among these are numbered various conditions affecting the nervous system (hysteria, psychosis, anorexia nervosa, *grand mal*); progressive myopia, keratoconus, alopecia areata; and arterial hypertension.

## PROTHROMBIN STUDIES

### Clinical Aspects

Not the least important of the many grave problems which may confront the clinician are those dependent upon an altered coagulability of the blood and manifested clinically by a variety of hemorrhagic states.

Until recently, the treatment of these varied hemorrhagic diseases has been conspicuous for its lack of success, a failure primarily and essentially due to an incomplete understanding of their etiology and mechanism. Within recent years, however, there has been an almost phenomenal progress in this field based upon the discovery and understanding of the antihemorrhagic factor known as vitamin K and upon an increasing knowledge of its essential relation to and influence upon blood coagulation.

For many years the most acceptable of the theories concerned with the mechanism of blood-clotting, and the one regarded as most plausibly explaining the observable phenomena exhibited in blood coagulation was that of Howell.

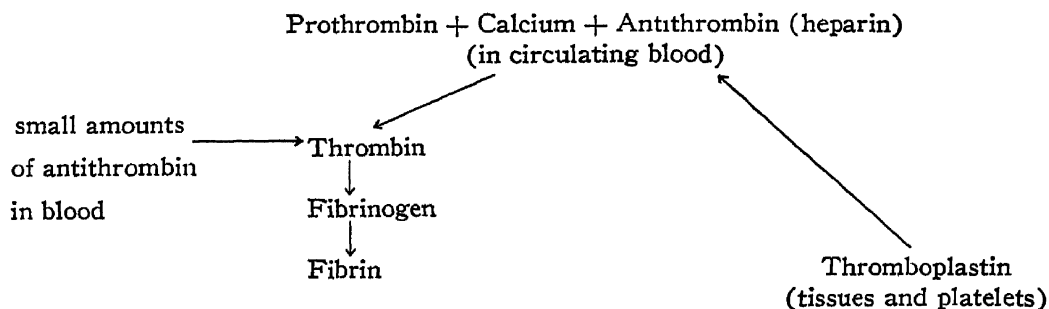
It long has been recognized that the transformation of shed blood from a fluid to a jelly-like mass is dependent upon the presence of a tangled mesh of fine fibrils which, by gradual shortening and

*fibrinogen* which, in shed blood, is transformed into an insoluble *fibrin* by the action of a ferment, *thrombin*. The precursor of this ferment is *prothrombin* which is converted into thrombin by the action of *calcium ions*.

From this theory, as so far stated, it is at once apparent that, as both ionized calcium and prothrombin are present in the circulating blood, there must be some provision to prevent intravascular clotting. In Howell's theory this factor is the presence of an *antithrombin* in the circulating blood which serves to prevent the interaction of calcium and prothrombin and hence the formation of thrombin. The presence of such a factor has been demonstrated and, because it has been found largely in the liver, it has been called *heparin*.

Now when blood is shed, a further factor — *thromboplastin* — is liberated, either from blood-platelets, injured tissue or both, which neutralizes antithrombin (heparin) and thus allows the formation of thrombin.

For the coagulation of blood 4 materials thus are essential: (1) *prothrombin*, (2) *calcium*, (3) *fibrinogen* and (4) *thromboplastin*, the interrelationship of which in Howell's theory may be simply shown in the following **scheme**:



contraction, embrace and hold the formed elements (corpuscles and platelets). These fibrils are spoken of as *fibrin*.

In Howell's theory, the precursor of *fibrin* in the circulating blood is a soluble

The antithrombin is neutralized by thromboplastin, allowing the formation of thrombin from prothrombin and thus permitting fibrin to be formed from fibrinogen. The small amounts of cir-

culating heparin are insufficient to overcome the action of the large amounts of thrombin produced

This, in brief, is the theory long accepted as best explaining the phenomena of blood coagulation. Rather recently, however, Mellanby and Mellanby and Pratt<sup>2</sup> summarized and elaborated investigations the results of which have brought about a radical revision of Howell's theory, and a coincident revision of its terminology

Having isolated prothrombin and thrombin in a relatively pure state and finding them to possess the characteristics of ferments, Mellanby terms them *prothrombase* and *thrombase*. Similarly, antithrombin becomes antithrombase and thromboplastin reverts to its former name, *thrombokinase*, first introduced by Morawitz in 1908

Mellanby's investigations demonstrated several variants in the theory proposed by Howell, *i. e.*, (1) that the presence of calcium ions is not essential for the conversion of prothrombase to thrombase; (2) that heparin is not, as Howell thought, an antiprothrombase (antiprothrombin) but an antithrombase (antithrombin)

In other words, instead of preventing the formation of thrombase from prothrombase, it is, on the contrary, an inactivator of thrombase once this substance has been formed, this inactivation being dependent upon the presence of neutral salts.

The failure of blood to clot within the vessels arises, not from the presence of heparin (which Mellanby believes not to be present in appreciable amounts in the circulating blood), but upon the fact that no thrombokinase is available for the conversion of prothrombase to thrombase. Heparin is present in the tissues but, according to Mellanby, acts only

as a local anticoagulant to prevent clotting in the small vessels

It is neutralized by thrombokinase and, hence, when heparin and thrombase are present in proportions sufficient to maintain blood fluidity, the addition of thrombokinase causes coagulation

In accordance with these investigations, the present most acceptable theory of blood coagulation may be diagrammed as shown on the following page

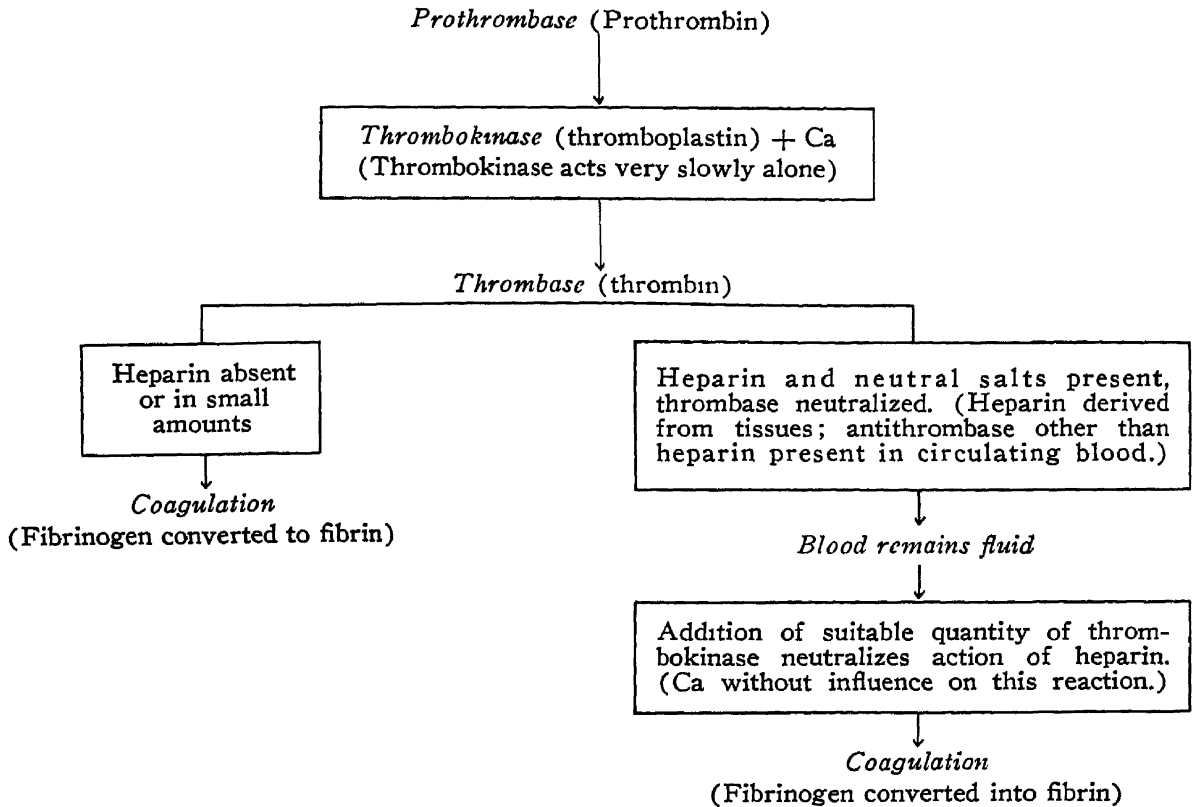
It should be said, however, that while the theory of Mellanby has gained wide acceptance, the mechanism of blood coagulation cannot be regarded as a closed issue but, on the contrary, is at present the subject of somewhat intensive study, many of its minutiae still requiring elucidation.

For example, there is good reason to believe that the importance of blood platelets in the initiation of coagulation has been overemphasized. According to Lenggenhager, the disintegration of blood-platelets in shed blood is a result, rather than a cause of coagulation, to support which assumption the spontaneous coagulation of platelet free bird plasma may be cited.

In this assumption he follows the theory proposed many years ago by Gratia and more recently again supported by Nolf<sup>3</sup> that the thromboplastic primarily responsible for coagulation is present in the plasma, any thromboplastic action of platelets being due to adsorption of the plasma factor from the surface of the platelet.

Evidence of the existence of such a plasma factor may be adduced from the work of Patek and Stetson who demonstrated that hemophilic blood becomes normally coagulable upon the addition of normal, cell-free plasma, apparently because of the presence of a plasma factor associated with the globulin fraction.

*Mechanism of Coagulation according to Morawitz (After Best and Taylor)*  
(Terminology of Howell is shown in parentheses)



Still further, the exact mechanism whereby thrombin converts soluble fibrinogen to insoluble fibrin is still largely speculative as also is the exact nature as well as the manner of production of heparin.

Overshadowing all other aspects of the studies of blood coagulation, however, are the intensive investigations concerning the antihemorrhagic factor, vitamin K, the existence of which was first postulated by Dam in 1929 and demonstrated by Dam and Schønheyder in 1934.

While engaged in a study of sterol metabolism in chicks, Dam was impressed with the occurrence of hemorrhagic manifestations coincident with a fat-free diet and later, with Schønheyder, described a deficiency disease resembling scurvy, investigations of which led to the discovery of the antihemorrhagic factor, vitamin K, a fat soluble vitamin appar-

ently necessary for the formation of prothrombin in the blood.

A rapidly accumulating volume of evidence based upon numerous and intensive studies has demonstrated the validity of Dam's original concept, has corroborated the existence and the essential importance of vitamin K in relation to hemorrhagic diseases, and has added a new and powerful weapon to the armamentarium available for therapeutic attack upon these conditions.

It soon became apparent that for the full development of such studies a method for the quantitative estimation of prothrombin which was more satisfactory and accurate than that hitherto in use was essential.

Prior to the investigations now to be discussed the method in ordinary use for the quantitative estimation of prothrombin was that proposed by Howell. This

method, devised by Howell in accordance with his theory of coagulation, was based upon the time required to produce coagulation of plasma in the presence of varying quantities of 0.5 per cent calcium chloride solution.

While proposed as a method for the determination of the prothrombin (reported as the "*prothrombin quotient*," obtained by dividing the time of the unknown by that of a normal simultaneously determined), Howell's method is, in fact, a determination of the coagulation time of recalcified plasma rather than accurate quantitative measure of prothrombin.

Methods in use at present derive from that described in 1935 by Quick, Stanley-Brown and Bancroft, which has been followed by various investigators and described by Quick<sup>4, 5</sup>; Brinkhous, Smith and Warner; Kato,<sup>6</sup> and others.

All of these methods are based upon the principle stated by Quick, that if all the other factors are made constant, the coagulation time of blood or plasma can be employed as a measure of the prothrombin concentration.

Quick presents the coagulation mechanism in 2 concise equations:

$$= \text{Thrombin}$$

$$\text{Prothrombin} + \text{Thromboplastin} + \text{Calcium} \\ \text{Fibrinogen} + \text{Thrombin} = \text{Fibrin}$$

If the coagulation time is proportional to the concentration of thrombin, it can be assumed that it is also proportional to the concentration of thromboplastin *provided* thromboplastin, calcium, and fibrinogen are made constant, as under these conditions the amount of thrombin formed is dependent upon the prothrombin concentration in the blood.

With this as a basis, Quick's method in essence consists in adding to oxalated plasma an excess of thromboplastin and then recalcifying with a fixed quantity of calcium chloride. The coagulation

time as thus measured is taken as a direct measure of the prothrombin concentration and evaluated by reference to a chart made by plotting the clotting time for known concentrations of prothrombin (Fig. 1).

It should be emphasized that the Quick method is one requiring considerable skill and experience and must be precisely and carefully executed if re-

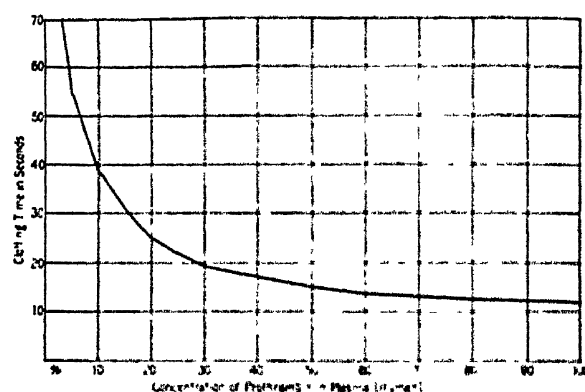


Fig. 1—Relationship of clotting time of recalcified plasma (with excess thromboplastin) to concentration of prothrombin. (Quick: *Am. J. Clin. Path.*)

sults are to be accurate and dependable.

This has been particularly noted by Magath<sup>7</sup> who has described in detail the minutia essential to a satisfactory technique, with particular emphasis upon the necessity for close and accurate temperature control and accurate timing.

The necessity for accurate, split second timing is obvious from the fact that if the normal time is 20 seconds, a clotting time of 30 seconds represents a marked abnormality. Magath has determined that there is a probable error of  $\pm 0.6$  second when the clot forms in 20 seconds; and a probable error of  $\pm 2$  seconds when the clotting time is 50 seconds. Furthermore, he believes that according to his own studies and those of Quick, a prothrombin time of 30 seconds suggests a prothrombin concentration of about 25 per cent of normal.



It is Magath's opinion that the results obtained by testing serial serum dilutions furnish a rough approximation rather than an accurate determination of the prothrombin present.

While Quick's method represents a definite and valuable advance, it possesses some inherent difficulties and disadvantages which without doubt will ultimately be overcome.

Among these may be mentioned the fact that the amount of blood required (4.5 cc.) increases the difficulties of applying the test to studies in infants; the fact that the preparation of thromboplastin is laborious and presents some technical difficulty; the fact that the thromboplastin solution is not particularly stable, although the stock powder keeps relatively well; and, as noted by Fullerton,<sup>9</sup> the difficulty of obtaining extracts of constant potency.

Pohle and Stewart<sup>8</sup> note that the variables in Quick's method may significantly affect the results. An important variable in this method is calcium, so that the optimal amount of calcium for recalcification must be determined in each instance. From studies of 85 normal individuals they report that with optimal recalcification, the normal prothrombin time is 10 seconds.

In their opinion the optimal calcium concentration is similar to normal serum calcium values.

They also find that as gross lipemia significantly shortens the prothrombin time, determinations should be made only on clear plasma.

All of these matters have been subjects of constant study so that it may confidently be expected that the method eventually will be simplified and robbed of much of its present technical difficulties.

Thus, Fullerton,<sup>9</sup> to obviate the variation in potency of thromboplastin ex-

tracts prepared from rabbit brain tissue, proposes the use of Russell viper venom (marketed by Burroughs and Wellcome under the name "*stypven*").

This preparation is ampouled in 0.1 mgm. amounts to which, before use, 1 cc. of sterile water is added. As it produces no coagulation in 24 hours when added to oxalated plasma, it has no thrombin-like activity.

The technic of prothrombin determination with cobra venom instead of thromboplastin derived from rabbit brain is that of Quick's method except that (a) for greater accuracy in measuring, 0.2 cc. (instead of 0.1 cc.) of plasma, calcium solution, and thrombokinase extract are used. (b) "*Stypven*" is used instead of tissue extract, using a solution prepared by dissolving 0.1 mg. of the dried venom in 1 cc. of distilled water.

Fullerton reports that determinations on the same plasma, using venom solutions from 2 ampoules, gave variations within 3 seconds or within the limits of experimental error. He finds the results with venom solutions comparable to those with tissue extracts and recommends that determinations be made upon diluted plasma as giving clearer readings and better differentiation.

Hobson and Witts<sup>10</sup> who have also used Russell viper venom in prothrombin determinations, comment upon Fullerton's observations and call attention to their own.

They remark that from various observations it appears probable that tissue extract thromboplastins, such as dried brain, consist of 2 factors: *thrombokinase* and *thrombokinase activator*. Commenting that clotting times are slow when snake venom alone is used and that the range of variation is thus greatly increased, as a result of which the results of the procedure in hemorrhagic diseases may be grossly misleading, they

emphasize the fact that Russell viper venom can be activated by lecithin, producing a reagent much more potent and active than any yet used in Quick's test.

While admitting that speeding up the reaction is not without disadvantage, they feel that a technic which will not give clotting times on the order of 12 seconds on human plasma probably has inherent defects. For this reason they feel that in conducting prothrombin determinations with viper venom, lecithin should be added as an indicator.

The modifications which they believe to be important are, briefly, the following:

1. The optimum dilution of the venom appears to be about 1:20,000. Samples of a single batch of venom are very constant, but different batches naturally vary.

2. Lecithin is prepared as a stock 10 per cent solution, of which 0.05 cc. is added to 1 cc. of the dilute venom solution, giving a concentration of 5 mg. per cubic centimeter.

This appears to be the optimum concentration for the particular lecithin they have used (Harrington's ovollecithin), but as various preparations may well vary in their activating power, the optimal proportion should be titrated for each sample.

Their procedure for the test, which is carried out at a temperature of 37 to 47° C., as in Quick's method, calls for the addition of 0.1 cc. of venom-lecithin reagent to 0.1 cc. of plasma, followed by the immediate addition of 0.1 cc. of calcium solution.

With different batches of venom and plasma, optimum prothrombin times of 8 to 11 seconds have been found.

The reaction may be slowed, if desired, by the use of higher venom dilutions, the lecithin concentration re-

maintaining standard at 5 mgm. per cubic centimeter.

In their studies, Hobson and Writts have used a venom preparation marketed as "Venox" (Boots).

As has already been noted, the fact that 4.5 cc. of venous blood is required for prothrombin determinations by Quick's method is a disadvantage in the use of the test in children or infants.

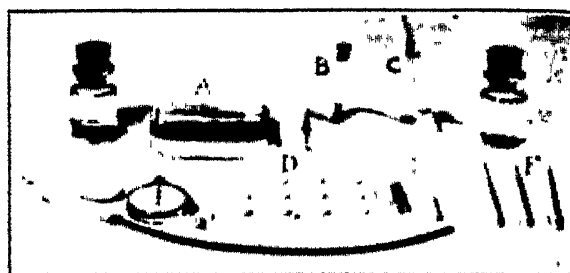


Fig. 2.—Utensils required for performance of microprothrombin test: *A*, Oxalated capillary blood in well of hanging drop slide, placed in a moist chamber; *B*, thromboplastin suspension; *C*, calcium chloride solution; *D*, porcelain spot plate; *E*, glass rod; *F*, three combination microhemopipettes (Kato, Ann. J. Clin. Path.)

To overcome this, Kato<sup>6</sup> has proposed a *micromethod*, employing capillary whole blood, a description of which follows.

The apparatus required for Kato's micromethod is shown in Fig. 2.

#### Reagents—

1. Thromboplastin. This is prepared from dried rabbit's brain, as in Quick's method.\*

2. Calcium Chloride Solution—1.11 Gm. of anhydrous calcium chloride dissolved in 400 cc. of distilled water.

The solution is stable, but concentration due to evaporation must be avoided.

3. Oxalate Solution—Potassium oxalate 0.75 Gm. and ammonium oxalate 1.25 Gm. dissolved in 100 cc. of distilled water.

Of this solution, 20 mm. are placed in the hollow of a hanging-drop slide and allowed to dry at room temperature.

#### Test—

1. Capillary blood is obtained by deep puncture of the heel (newborn and premature).

\* Thromboplastin powdered and ampouled is now commercially available (Difco Laboratories).

ventral surface of the big toe, or the ear-lobe or finger-tip. The blood should flow freely without squeezing

2. Approximately 0.2 cc of blood is collected in a pipette, transferred to the prepared slide, and at once thoroughly mixed with the dry oxalate by rotation of the slide or with a fine glass rod. The slide is then placed in a moist chamber (Petri dish containing moist filter paper) until the test is performed

3. With a combination microhemopipette, devised by Kato, exactly 10 cmm each of thromboplastin suspension and 1/40 M calcium chloride solution are measured and mixed together in the well of a clean hanging-drop slide

If only 1 pipette is available, it should be thoroughly flushed with normal saline solution between each use

For mixing, a white porcelain spot plate is convenient and allows the performance of several tests in succession

4. To the thromboplastin-calcium chloride mixture, 10 cmm of well-homogenized oxalated whole capillary blood are now added, at the same instant starting a stopwatch

*All reagents must be at room temperature when used*

5. With a fine glass rod, the mixture is agitated for 5 to 6 seconds to ensure thorough mixing

The end-point is the formation of a gelatinous clot, evidenced by the formation of fibrin and the fixation of the mass and must be noted by the stopwatch

With this method the average normal prothrombin time is 20 seconds, with a deviation of  $\pm 2$ .

As prothrombin undergoes relatively rapid deterioration, the determination should be made as soon as possible after withdrawal of the blood. The amount of blood in Kato's method will allow several dilution tests (25, 50 and 75 per cent) so that a dilution curve can be made.

As the clotting time of oxalated blood after the addition of thromboplastin and calcium chloride solution is inversely proportional to the concentration of prothrombin, a curve of normal correlation may be obtained by plotting the coagulation time against the percentage of dilution.

Such a curve may then be used as a guide to the determination of prothrom-

bin concentration in pathological blood.

Bray and Kelley,<sup>11</sup> in prothrombin studies on the newborn, used blood obtained from heel puncture and from the fontanel (superior longitudinal sinus).

Blood was collected in test-tubes, 10 x 75 mm, without lips, containing 0.05 cc of M/10 sodium oxalate and marked at 0.5 cc. capacity, shaking to prevent clotting.

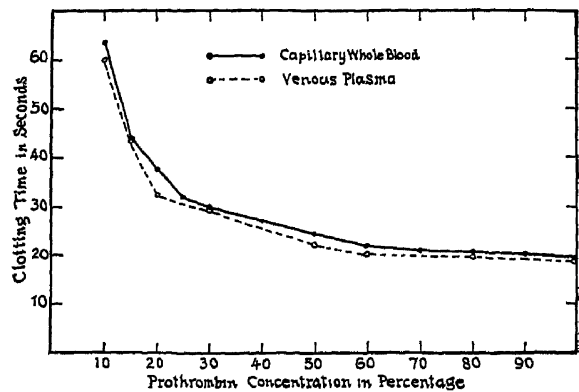


Fig 3—Prothrombin dilution curves constructed from data obtained by plotting coagulation time of each dilution against percentage concentration of prothrombin in original blood and plasma (Kato: Am. J. Clin Path)

Ziffren, Owen, Hoffman and Smith<sup>12</sup> describe a simple method used by them as a *bedside test for the control of vitamin K therapy*, for which thromboplastin is the only reagent required. Their procedure follows:

1. Into an ordinary 10 x 75 serological test-tube marked at 1 cc. capacity, place 0.1 cc. of thromboplastin solution prepared from rabbit brain.

2. Blood secured by venipuncture is added to the 1 cc. mark, the tube inverted over the finger once or twice and then tilted every 1 or 2 seconds until clotting occurs

3. The same procedure is carried out on normal blood and a calculation made according to the formula:

$$\frac{\text{Clotting time of normal blood}}{\text{Clotting time of patient's blood}} \times 100 = \text{clotting power in per cent of normal.}$$

Certain precautions are advised. The thromboplastin should be of such potency that a clot is obtained with normal blood in 25 to 50

seconds. If longer than 50 seconds, the thromboplastin should be discarded, if more rapid than this, an appreciable error is introduced by the time required to mix the blood and thromboplastin. If the clotting time is less than 25 seconds, the thromboplastin may be adjusted to give control readings within the desired range by dilution with normal saline.

While the blood should be transferred from the syringe to the test-tube promptly, a delay of 30 to 90 seconds does not appreciably interfere with the result.

As, for reasons unknown, traces of thrombin accelerate the reaction, samples should always be drawn with newly sterilized equipment, without delay and as far as possible free from bubbles. When great difficulty is encountered in entering the vein, the sample is not apt to be satisfactory because of the presence of traces of thrombin.

The test should be made at ordinary room temperature, warming the syringe and test-tube in the hand if the room temperature is low.

Ziffren and his associates believe that, unless the potency of the thromboplastin is constant, the expression of the prothrombin time in seconds is unreliable and for that reason prefer reporting in reference to a normal sample.

As they have previously pointed out,<sup>13</sup> their bedside method, like that of Quick, is a one-stage method, measuring not only the amount of prothrombin but also the ease with which it can be converted into thrombin. As both the amount of prothrombin and the "convertibility" may vary while the summation of the two represents the measure of the tendency to bleed, they believe this summation more important than the isolated determination of prothrombin alone as in the two-stage methods. (Warner, Brinkhous and Smith and Smith, Warner and Brinkhous.)

Among the numerous studies of the procedure described by Quick, that of Kaump and Greenwood<sup>14</sup> is of interest.

According to Quick's concept of the mechanism of clotting (prothrombin + thromboplastin + calcium = thrombin;

thrombin + fibrinogen = fibrin [clot]), if an excess of thromboplastin and calcium are added to plasma, the only variable factor is the prothrombin. According to this concept, he considers the prothrombin time to be the duration of the interval from the addition of the calcium chloride to the formation of a clot. As Kaump and Greenwood point out,

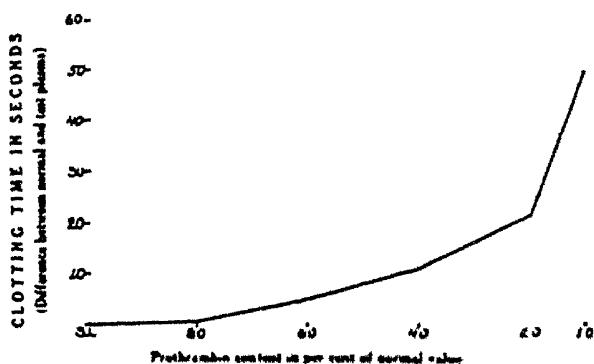


Fig. 1. Clotting time for varying plasma (prothrombin) content. (Kaump and Greenwood: *Am. J. Clin. Pathol.*)

however, this reaction is not only the index of the time required for prothrombin, thromboplastin, and calcium union to form thrombin, but also includes the time required for the conversion of thrombin and fibrinogen to fibrin, so that Quick's method represents the summation of the time involved in the entire clotting process.

From their investigations, Kaump and Greenwood conclude as follows:

(1) The optimum concentration of calcium chloride is 25 per cent, of thromboplastin 25 per cent, and of plasma 50 per cent, and recommend that they be used in these proportions. In actual practice, with a total volume of 1 cc., they thus use 0.25 cc. of calcium chloride, 0.25 cc. of thromboplastin, and 0.5 cc. of plasma.

(2) While variations in temperature admittedly affect clotting time, they do not believe the meticulous temperature control described by Magath<sup>7</sup> to be essential.

In their experience, a room temperature of from 70° to 80° F. (21.1° to 26.7° C.) suffices for clinical purposes.

(3) They were unable to corroborate Quick's "normal" reaction time of 12 to 15 seconds and consider 19 to 24 seconds as normal.

(4) They emphasize the necessity for normal controls run at the same time as the test proper and of expressing the prothrombin content in terms of percentage of normal.

For this purpose they use the chart shown in the Fig. 4 based upon the difference between normals and test plasmas, expressed as the percentage of normal.

Their chart is similar to that of Quick's, but whereas his chart is based upon determination of the clotting time in seconds, their chart is constructed by using calcium chloride and thromboplastin in constant amounts and adding normal saline to replace gradually decreasing amounts of plasma.

While it is apparent from the foregoing discussion that the ideal method for the laboratory study of hemorrhagic diseases has, perhaps, yet to be found, it is also apparent that the newer prothrombin studies coupled with the elaboration of the antihemorrhagic factor vitamin K constitute a great and even phenomenal advance toward their ultimate understanding.

Obviously, the first step toward the intelligent interpretation and clinical application of prothrombin studies is an understanding of what constitutes the normal and the normal range of variations of prothrombin determinations. Many investigators have been occupied with this phase of the subject.

In view of the importance of prothrombin determinations in the hemorrhagic diseases encountered in the newborn and infants, many studies have

been reported upon the normal prothrombin time in this group.

Bray and Kelley,<sup>11</sup> from a study of 23 *newborn*, report upon the range and average of prothrombin time during the first week, in which daily determinations were made. They conclude that the prothrombin time varies widely in the newborn, normally tending to fall within the normal adult range on the day of birth, rising between the second and fifth days to a peak definitely higher than the adult normal range, and then becoming stabilized within the normal adult range after the fifth day.

These authors found no significant relation between the prothrombin time and the platelet count in the newborn.

The prothrombin time of cord blood is generally low and somewhat below that of blood taken within 24 hours after birth, but still remains within the normal adult average.

Contrary to these observations, Kugelmass reports the newborn prothrombin level as about one-fourth that of adult blood, the adult level not being reached until the blood volume has reached about 1 liter.

He comments, however, that this is an apparent rather than an actual deficiency as, under normal conditions, a dram of newborn blood contains sufficient prothrombin to clot the entire volume of circulating blood. He emphasizes, therefore, that since there is normally sufficient reserve in prothrombin to fulfill clotting function in the newborn, there is no necessity for routine administration of vitamin K for the purpose of bringing the prothrombin level in the newborn to that of the adult. He further states that as the reserve prothrombin level of older infants and children is apparently unaffected by an increased intake of vitamin K, an adequate diet appears to provide sufficient vitamin K to produce

considerably more than the amount necessary to arrest hemorrhage in normal infants and children.

Norris and Rush,<sup>15</sup> from a comparative study of 50 *mothers* and 51 *babies*, using Quick's method of prothrombin determination, report levels above normal in the mothers and somewhat below normal in the infants.

These observers recommend that control determinations be made upon pooled specimens and also consider a 25 per cent plasma dilution conducive to more accurate comparisons.

Rush<sup>16</sup> reports upon a further study, comparing 18 samples taken at delivery with 6 normals in which prothrombin and fibrinogen determinations of cord blood at delivery were compared to those of the maternal blood.

In the cord bloods, the fibrinogen levels of the plasma fell within the normal range, while the prothrombin levels were below normal. The prolonged prothrombin time of cord blood was thus not due to fibrinogen deficiency.

In maternal blood, both prothrombin and fibrinogen were above normal.

Kato<sup>17</sup> studied the prothrombin clotting time of 173 *newborn infants* (mature and immature) using his micro-method.

From an aggregate of 1595 determinations made during the first 4 weeks of postnatal life, he reports that in 100 mature infants the average prothrombin time on the day of birth was 43.2 seconds. As the infants grew older, the time gradually shortened, reaching 25 seconds (average) on the tenth day.

In 73 *immature infants*, the average was 46.5 seconds and showed much greater variation on the subsequent days than occurred in mature infants. In this group, in some instances, the prothrombin time increased after birth, a prolonged prothrombin time in 1 instance

being associated with a strangulated hernia.

No correlation was apparent, at least on the day of birth, between the prothrombin time and the degree of maturity or immaturity of the infant.

Kato comments that the most important clinical inference arising from this study is that the average *newborn infant* possesses a smaller fraction of prothrombin complement than the adult, which would explain satisfactorily the occurrence of conditions grouped as hemorrhagic disease of the newborn (melena neonatorum, omphalorrhagia, hematuria, hematemesis) and, perhaps, in some measure, intracranial hemorrhage from birth trauma.

He also notes, as a possibly significant factor in determining the results in his series, the dietary habits of the mothers, the majority of whom came from the lower social strata.

Hause and Tocantins<sup>18</sup> report upon the variation of plasma prothrombin time in *normal men and women*. The significant findings of this study were, briefly, that there were no consistent variations in women which could be correlated with any phase of the menstrual cycle; that certain normal men may have consistently high plasma prothrombin concentrations as compared with other normal men simultaneously observed, as a consequence of which the desirability of employing 2 or more normals as controls when determining the prothrombin percentage of normal plasmas becomes apparent.

These authors believe that at least 2 and preferably 3 controls should be used to establish the time equivalent to 100 per cent prothrombin with a given thromboplastin solution.

While it appears from the reports which have been briefly summarized, and which in effect represent but a tithe of

the studies made, that there is still much work to be done before methods and normal changes can be said to be satisfactorily and permanently standardized, nevertheless the importance of prothrombin studies in the study of hemorrhagic diseases and as an aid in their clinical diagnosis and prognosis is clearly established.

It now has been shown that prothrombin is formed in the liver from vitamin K, which has further been identified as a naphthoquinone. Still further, it has been shown that the precursor of prothrombin (vitamin K) is formed in the intestinal tract, as a result of bacterial activity, and must be absorbed from the intestinal tract before it can be transformed by the liver into prothrombin, for such absorption both a normal fat metabolism and the presence of bile salts being essential.

These facts are of essential interest and importance in the understanding of the mechanism of hemorrhagic diseases and tendencies.

Quick<sup>19</sup> suggests the absence of bacterial activity in the intestinal tract of the *newborn*—and hence the absence of factors essential to the formation of vitamin K—as a probable cause of those hemorrhagic diseases of the newborn known to be associated with prothrombin deficiency.

Similarly, diseases reflected in disturbances of fat metabolism or bile production quite logically may be expected to be complicated by hemorrhagic tendencies. In such conditions, prothrombin studies are of definite interest and value though, as Haden and Schneider<sup>20</sup> point out, the careful study of hemorrhagic disease calls for various laboratory studies in addition to prothrombin determinations. They list these as: (1) Routine complete blood count (hemoglobin, red blood count, white blood count, color

index, and study of stained smear); (2) coagulation time; (3) bleeding time; (4) platelet count; (5) clot retraction; (6) prothrombin time.

Under certain conditions, plasma clotting time, fibrinogen content, and a capillary resistance (Rumple-Leede) test are also advisable.

Prothrombin determinations have naturally come into wide use in connection with the study of diseases associated with *jaundice*, especially when surgical intervention is under consideration, not solely or indeed primarily as a measure of liver function—for which there is as yet no truly satisfactory laboratory procedure, or even combination of laboratory procedures—but essentially as an aid in guarding against the hemorrhagic tendency associated with jaundice.

DeLor and Reinhart,<sup>21</sup> from a study of various liver function tests, among them prothrombin determinations, in 381 cases, conclude that prothrombin is universally diminished when liver function is reduced 50 per cent or more, as shown by the hippuric acid test.

The mechanism responsible for the hemorrhagic tendency in jaundice has long been a clinical enigma and an anathema to the surgeon because, while, as Quick<sup>22</sup> points out, the incidence of serious hemorrhage is relatively low, the gravity of the problem lies in its unpredictability with any degree of certainty by clinical means or any of the laboratory methods heretofore in common use.

The importance, therefore, of prothrombin determinations in this problem is readily apparent.

In various types of jaundice, it has been found that prothrombin may drop to a very low level, the bleeding tendency being associated with the prothrombin deficiency. Fortunately, however, it has also been found that nearly 86 per cent of prothrombin may be lost before seri-

ous hemorrhage occurs, so that there is a wide margin of safety.

While as yet vitamin K deficiency has not been clearly demonstrated as a cause of *hemorrhage* in man, its etiologic relation to hemorrhage appears logical and highly probable.

The permanent cure of hemorrhagic tendencies appears to depend upon the restoration of normal hepatic function, but as a temporary measure, *blood transfusion* is indicated in all types of prothrombin deficiency associated with bleeding as a prompt though transiently effective measure.

Cullen, Ziffren, Gibson and Smith,<sup>23</sup> extending observations previously made in animals, report that *chloroform anesthesia* produces a fall in the plasma prothrombin in man but that no such effect followed ether or cyclopropane anesthesia in uncomplicated cases. They conclude, therefore, that the postoperative fall in plasma prothrombin observed in patients with obstructive jaundice or biliary fistulas is evidently due essentially to factors other than the anesthetic agent itself.

While inclined to attribute some possible relation of anesthesia to the failure of vitamin K therapy to combat effectively the postoperative prothrombin level, Quick<sup>5</sup> also recognizes the possibility that trauma and perhaps other, not clearly defined, factors cause a temporary damage of the liver, resulting in all impaired synthesis of prothrombin.

Walters<sup>24</sup> agrees with other observers that the hemorrhagic disturbances in jaundice are associated with and related to the absence of the "coagulation vitamin," the hypothetical fat-soluble vitamin K, and also to the exclusion of bile acids from the intestinal tract.

Stewart,<sup>25</sup> reporting a fall in the plasma prothrombin and a coincident rise in plasma fibrinogen in a patient

developing bilateral pneumonia while receiving vitamin K therapy for severe hemorrhage, speculates upon the effect of infection.

A recent report by Rhoads and Fiegelman<sup>26</sup> concerns the use of a synthetic vitamin K substitute, *2-methyl-1-4-naphthiquinone*, in the treatment of prothrombin deficiency. There were no toxic effects observed in 10 patients. In 3 cases *hemorrhagic tendencies* were controlled and good results were also obtained in 2 cases of *obstructive jaundice*.

Similar favorable reports of the use of this substance have been made by Frank, Hurwitz and Seligman<sup>27</sup> and also by Andrus and Lord.<sup>28</sup>

In relation to the hemorrhagic diseases of infancy and childhood, Kugelmass believes that prothrombin deficiency is not a determining factor except in the relatively rare, latent, or manifest hemorrhagic diseases of the newborn, *icterus gravis neonatorum*, *pseudohemophilia hepatica* and occasionally in *hereditary pseudohemophilia*, the alleviation of which by *vitamin K therapy* is effective for the former 2 and possibly for the latter 2 types of blood disorders.

The studies in this field now vigorously pursued by many investigators occupied with varied aspects of the general problem bid fair to warrant the assumption that much of the mystery and the clinical difficulty long associated with hemorrhagic tendencies may ultimately, and perhaps even in the near future, be dispelled.

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## RENAL FUNCTION, RENAL DISEASE AND HYPERTENSION

### Newer Aspects

From the standpoint of the practitioner, the most important single factor concerned with renal disease concerns



its diagnosis. Similarly, the most important *clinical* aspect of renal function is the fact that, before any functional limitation or deficiency can be definitely detected, approximately 75 per cent of the renal substance must be so definitely damaged as to be incapable of function, if not, indeed, altogether destroyed.

It is for this reason that the all-sufficient, ideal test of renal function has yet to be found and reliance must be had upon many, none of which in all respects is entirely satisfactory.

The most frequently employed procedure designed to secure information concerning renal activity is the urinalysis, and the most common abnormality thus encountered in varying degree is albuminuria. But while massive albuminuria is definitely generally pathologic in significance, this is not nearly so often nor nearly so certainly true in the case of mild albuminuria.

It is now rather generally recognized that mild albuminuria is not *necessarily* the concomitant of renal disease nor the inevitable precursor of its advent. It may, indeed, be not infrequently seen in the normal young adult as an aftermath of vigorous or sustained physical exertion when it is regarded as, in general, of physiologic origin and unrelated to the presence of renal disease and true renal dysfunction.

When albuminuria, irregular in occurrence and mild in degree, occurs, however, in connection with hypertension, there is good reason to believe that neither the hypertension nor the albuminuria can be regarded as of no moment or dismissed with equanimity. On the contrary, recent studies suggest that the hypertension cannot safely be regarded as essentially benign, while the albuminuria may well be significant of early renal impairment.

Among the more recent studies is that of Brucer and Robinson<sup>29</sup> here briefly summarized.

In a study of 2009 men and 500 women, in whom only a single urinalysis was done, it was found that as the level of pressure increased, the incidence of albuminuria also increased.

Because of the fact that there was but a single urinalysis, and also because in their series only 23.4 per cent had a blood-pressure over 180 mm., and only 6.3 per cent had a pressure above 200 mm., this incidence of albuminuria represents the minimal rather than the average incidence to be expected.

While a relation between hypertension and albuminuria has long been clinically accepted, proof of this practical assumption has only recently become available, largely through the work of Goldblatt and his associates in the demonstration of the effects of experimentally induced renal ischemia.

The present focus of interest now rests largely in the query which comes first. Does the change in the renal parenchyma *per se* produce the hypertension, or does the hypertension *per se* influence the change in the renal parenchyma?

As a contribution to the study of this phase of the problem, Brucer and Robinson studied the incidence of albuminuria in those over 40 and those below this age.

Among the men there was a far greater incidence of albuminuria in those over 40, suggesting that hypertension comes first. The validity of this assumption is somewhat shaken, however, by the fact that, in this series, the ratio between young and old hypertensives was completely reversed in the women. The reason for this discrepancy thus far is not apparent.

In the series reported upon by these authors several facts of interest and practical importance developed. Not only did it appear that a raised blood-pressure is accompanied by albuminuria in a great many cases, but also, the more severe the albuminuria, the greater the probability of hypertension. Furthermore, there was a very striking association between the blood-pressure level and the incidence of albuminuria which increased *pari passu* with the rise in blood-pressure.

Sex, also, showed definite variations, the incidence of albuminuria being 4 times greater in hypertensive men than women. A definite relation between diastolic hypertension in twice as many hypertensive men as in the low pressure group, while it was seen also in 11 per cent of women with diastolic hypertension. Studies of body build showed a common association between obesity, hypertension and albuminuria.

Bruce and Robinson comment that the older tendency to regard hypertension as a syndrome rather than a pathologic entity is changing and remark, with good reason, that their justification for the assumption that a departure from normal of any physiologic measurement, especially that of blood-pressure where a departure from normal is rather constantly associated with an increase in morbidity and mortality, may well be assumed to signify an organic change.

In a somewhat different discussion of renal dysfunction, Leiter<sup>30</sup> also emphasizes the importance of careful evaluation of the significance of albuminuria in the young adult. Discussing also the diagnostic difficulties encountered in the differential evaluation of hypertension, and particularly of "*essential hypertension*," Leiter wisely comments that this latter is more properly made after, and not before, the *complete* examination of the patient.

Much of the diagnostic difficulty encountered in the study of cases falling within the groups discussed arises from the lack of fully satisfactory tests of renal function. Barker<sup>31</sup> lists the following as of clinical value and utility. The *dilution and concentration tests*, the former being the safer and most useful under all conditions usually encountered, the *P S P test* and the *urea clearance test* of Van Slyke.

In addition to being technically simple and practically without contraindication, the P S P test is definitely useful. As Barker comments, however, its usefulness and clinical value are in direct proportion to the clinical appreciation of its limitations.

Thus, in the presence of congestive heart-failure, where passive congestion of the kidneys and liver interfere with the normal distribution and movement of the dye, a low excretion is to be expected and cannot *per se* be taken as evidence of renal damage and dysfunction.

On the other hand, an excretion of 90 per cent or over cannot necessarily be regarded as "normal." Such a finding may well suggest the possibility of hepatic cirrhosis, as in this condition the prerenal deviation of the dye is prevented so that nearly all is passed through the kidney. Hyperthyroidism and certain cases of hypertension with vigorous circulation may also show high dye excretion, returning to normal levels with alleviation of these conditions.

The urea clearance test, requiring a well equipped and completely staffed laboratory, is less suited to the needs of the clinician at large but may well be resorted to in cases showing definite abnormalities in the tests already mentioned.

Among the newer tests of renal function is that recently introduced by Exton and Rose<sup>32</sup> as "*a 1-hour renal condition*

*test.*" This procedure is not a functional test in the sense that it measures dye elimination or a clearance, but rather a test of diagnostic and prognostic significance involving both function and organic status of glomeruli and tubules; hence a test of renal condition.

The directions for the Exton-Rose procedure are from their paper:

#### RENAL CONDITION TEST

*Preliminary Instructions for Patients*—"For at least 15 hours preceding the test do not take any medicine or alcohol at all and as little water, tea, coffee or other drinks as you can. When necessary for comfort, try to relieve thirst by taking only a mouthful of water at a time.

"For at least 3 hours preceding the test do not drink anything at all even if you are thirsty"

*Directions for Collecting Urine*—"Time the start of the basal hour immediately after the patient empties the bladder and time the end when the patient begins to empty the bladder. Discard the first and measure and preserve the second sample for analysis. Throughout the hour bed and suspected orthostatic cases should remain recumbent and ambulant rest quietly in a chair.

"It is sometimes desirable to extend tests over a second or active hour. In doing this, time the start of a second hour immediately after the basal sample is voided, and the patient drinks 300 to 400 cc. of water, and time the end when the patient begins to empty the bladder. Measure and preserve the sample for analysis. Throughout the active hour patients should maintain activity like walking or similar standing exertion. After the test, take the blood-pressure and then a blood sample.

"The second hour may be varied to test the effects of dilution, drugs, posture, etc., but a basal hour sample suffices for almost all of the cases.

"When it is necessary to shorten or exceed an hour for any reason, calculate excretions to actual output per minute and multiply by 60, so that all reports are uniform in terms of hourly rates of excretion."

The laboratory requirements of the Exton-Rose procedure may be restricted to determination of the reaction and specific gravity and quantitative determina-

tion of protein and formed elements as a minimum, but, in accordance with the nature of the clinical problem, may be expanded to include albumin and globulin in blood and urine, hemoglobin and blood cholesterol, fibrinogen or other constituents, such as nonprotein nitrogen.

In this procedure the significance of the specific gravity is the same as in any other concentration test.

Since protein raises specific gravity, a correction must be made in the presence of high protein concentrations: for every 350 mg. per 100 cc. subtract 1 point in the last place.

Anything less than 30 cc. in volume is regarded as tending to oliguria and anything over 55 cc. per hour as tending toward polyuria.

For formed elements, the following high normal limits are adopted:

Casts per hour . . . . .	1,000
Red cells per hour . . . . .	100,000
White cells per hour . . . . .	200,000

For the significance and correlation of the various blood determinations with the urinary findings, the original paper should be consulted.

#### SPUTUM STUDIES IN PROGNOSIS OF PNEUMONIA

The importance of pneumococcus typing from the sputum in the specific therapy of pneumonia is well recognized but that this procedure may also furnish information of prognostic significance has only recently been suggested.

In a preliminary report of studies made in 78 cases, Frisch<sup>33</sup> called attention to a correlation between multiple lobe involvement, leukopenia, incidence of blood stream invasion and the number of extracellular pneumococci in rusty or bloody sputum, and suggested that this

TABLE I  
(After Frisch)

112 CASES SHOWING NO MORE THAN 10 PNEUMOCOCCI *per* OIL IMMERSION FIELD AT ANY TIME DURING PRODUCTION OF RUSTY OR BLOODY SPUTUM

Type	Cases	Bacteriemia	Leukopenia <sup>*</sup>	Multiple Lobes	Expired
I	30	5	2	8	1
II	20	1	0	10	1
IV & V	4	0	0	0	0
VII ...	19	4	1	6	0
VIII	16	1	2	2	0
Others ..	23	5	4	7	1
Total .	112	16	9	33	3
Per cent. .	.	14	8	29	3

\*Less than 10,000 during acute stages

TABLE II  
(After Frisch)

48 CASES SHOWING 11 TO 35 PNEUMOCOCCI *per* OIL IMMERSION FIELD IN ONE OR MORE SPECIMENS OF RUSTY OR BLOODY SPUTUM

Type	Cases	Bacteriemia	Leukopenia	Multiple Lobes	Expired
I ...	7	4	2	2	0
II ... ..	18	8	3	5	3
IV & V. . .	8	4	0	3	0
VII . . . .	7	3	0	1	1
VIII ... .	3	2	0	2	1
Others. . .	5	3	0	3	0
Total.....	48	24	5	16	5
Per cent . . . . .		50	10	33	10

TABLE III  
(After Frisch)

44 CASES SHOWING MORE THAN 35 PNEUMOCOCCI *per* OIL IMMERSION FIELD IN ONE OR MORE SPECIMENS OF RUSTY OR BLOODY SPUTUM

Type	Cases	Bacteriemia	Leukopenia	Multiple Lobes	Expired
I ... . . .	11	7	6	5	7
II.....	16	12	6	13	12
IV & V....	1	1	0	1	1
VII ... . .	7	5	2	2	4
VIII. ....	4	3	1	2	1
Others ... .	5	3	2	5	3
Total.... .	44	31	17	28	28
Per cent.... .	.....	70	39	64	64

last factor might serve to differentiate mild and severe cases. A further study of 228 cases<sup>34</sup> indicates that the procedure is of value as a prognostic indication and for this reason is here briefly summarized.

The rationale of the procedure proposed by Frisch is based upon studies from the results of which it appears, first, that there is a significant correlation between the number of pneumococci *per* field in the sputum and the incidence of bacteriemia, leukopenia, multiple lobe involvement and the mortality rate; and, second, that the number of pneumococci in rusty sputum is a reflection of the number of pneumococci in some pneumonic areas of the lung.

The basis for this concept appears from the data in the 3 tables on the preceding page.

From the data shown in the tables it is readily apparent that as the number of pneumococci per oil immersion field increased there was a parallel increase in the frequency of bacteriemia, multiple lobe involvement and leukopenia—all factors of unfavorable prognostic import. This is also quite evident in the difference between the mortality rate of 3 per cent in the cases showing less than 10 pneumococci per oil immersion field as compared to a mortality rate of 64 per cent in the group showing more than 35 pneumococci per field.

It would appear that merely by the additional notation, in the course of the routine Neufeld typing procedure, of the number of pneumococci per oil immersion field, not only may the mild case be distinguished from more severe requiring aggressive therapy, but rather reliable prognostications of the outcome are possible.

Thus, in 181 proven cases, Frisch was able to give an accurate prognosis from the first sputum specimen in 85 per cent,

the remaining 15 per cent requiring 2 or more slides.

From the studies reported the following prognostic formulas are suggested:

Less than 35 pneumococci per oil immersion field . . . . .	Recovery
More than 35 but less than 100 . . . . .	Serious
100 or over . . . . .	Fatal

In the second group classified as serious, the final prognostication as to the outcome was based upon sputum studies following the institution of specific serum therapy. If, under treatment, the pneumococcus count decreased, a favorable prognosis was given. If, on the contrary, the pneumococcus count progressively increased over 65, a fatal prognosis was indicated.

To these general rules there were 2 exceptions. Type II cases which were classified as serious when the pneumococcus count was more than 20 per field, and the ultimate prognosis held in abeyance until the effect of serum therapy could be determined by further sputum studies; and Type III pneumonias which will be discussed in some detail below.

The atypical behavior of Type III pneumonia has been recorded by numerous observers. In addition to its predilection for the aged, it is characterized by its relatively prolonged clinical course, relatively low bacteremic incidence, and the unusually high mortality associated with bacteremia when this occurs.

Bacteriologically, the Type III pneumococcus is distinguished by its extremely thick capsule and hence by its production of large amounts of specific soluble carbohydrate. Clinically, Type III pneumonia is characterized by the comparatively unsatisfactory response to serum therapy. From the standpoint of the sputum studies here discussed, in fatal cases of Type III pneumonia the pneumococcus count was not high but,

on the contrary, consistently low and hence could not be used as a reliable basis for prognostic dicta.

In the course, however, of studies particularly directed toward Type III pneumonias<sup>35</sup> it was found that prognostic

cimens into 2 general groups, "reticulated" and "nonreticulated."

In the "nonreticulated" group the background is rather uniformly pink and generally granular. In the "reticulated" group the background is composed of a



Fig. 5—"Nonreticulated" Type III sputum on left; "reticulated" sputum on right (Frisch: Am. J. Clin. Path.)



Fig. 6—Note interconnecting strands of capsular material passing from one organism to another. (Frisch: Am. J. Clin. Path.)

indications could be based upon appearances in sputum smears which were related to the amount of specific soluble carbohydrate present.

When sputum smears from Type III pneumonia are stained with Wright's stain it is possible to separate such spe-

coarse, branching reticulum taking a bluish-red stain like that of the capsules of the interspersed pneumococci.

It has long been recognized that direct sputum typing by the Newfeld method is often complicated by the gelatinous character of the sputum arising from the

TABLE IV  
(After Frisch)

Group	Cases	Average Age	Bacteremia %	Leukopenia* %	Multiple Lobes	Mortality %
Nonreticulated	33	44	7	32	39	9
Reticulated	24	51	65	40	70	83
Total	57	48	30	35	52	40

\*Less than 10,000 during acute stages

large amount of specific soluble carbohydrate present. For this reason such specimens are frequently diluted with normal saline prior to direct typing.

Frisch, however, describes a method whereby not only is direct typing possible without dilution, but also the demonstration of reticulation.

The method is simple: Rusty sputum is smeared on a slide, air dried, and then over a small area of the slide layer with specific typing serum and a drop of methylene blue.

When so treated, not only will typing be satisfactory but the quellung reaction may be of an unusual and hitherto undescribed character in that the capsule of one organism may be connected to that of another by long strands of capsular substance (Fig. 6).

In addition, in such smears masses of free capsular substance may be seen as greenish-gray material without the presence of pneumococci (Fig 7).

That this "reticulation" is due to the presence of specific soluble carbohydrate is shown by the fact that it can be produced as desired in sputum from any type of pneumonia by the addition to such sputum of SSSIII but not by the addition of specific soluble substance from other types.

From these studies the concept emerged that a differentiation between mild and potentially severe cases of Type III pneumonia could be predicated upon

the presence or absence of reticulation in sputum smears prepared as above described.

That such a concept has some validity is shown in Table IV in which the incidence of bacteremia, leukopenia and multiple lobe involvement are correlated with the incidence of reticulation and

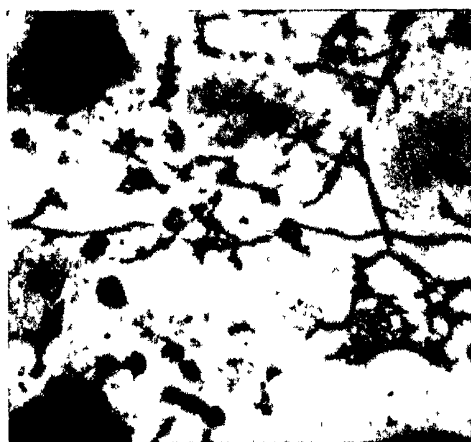


Fig 7—Wright stained smear from lung of an autopsied case of Type III pneumonia. Note reticulation passing from capsule of one pneumococcus to that of another. (Frisch. Am. J. Clin. Path.)

nonreticulation in 57 cases of Type III pneumonia.

In the series studied by Frisch there were 2 cases of pneumonia due to *B. Friedländer*. This organism also is noted for its heavy capsule and also showed a typical reticulation in Wright-stained sputum smears.

From these studies it is shown that, in contradistinction to other types, in

Type III pneumonia prognostic indications are based, not upon the number of pneumococci per field, but upon the amount of specific capsular carbohydrate as indicated by the presence and degree of reticulation in the background of the sputum smear both as typed, by the procedure above described, or when stained by Wright's stain.

In all types it should be noted that studies must be carried out on typically "rusty" or bloody sputum.

the necessity for adequate criteria for the diagnosis of staphylococcemia.

In addition to the clinical signs and symptoms indicative of clinical septicemia, the presence of living staphylococci in the circulating blood must be established with reasonable certainty. While the post-mortem demonstration of multiple pyemic lesions containing staphylococci, or similar findings demonstrated by operation during life, is adequate and reliable proof of staphylococcemia,



Fig. 8—Reticulation in *B. Friedlaender* pneumonia (Frisch, Am. J. Clin. Path.)

## STAPHYLOCOCCEMIA

While bacteriemia is justly regarded as a symptom of grave significance, staphylococcus bacteriemia has long been looked upon as a condition for which efficient methods of treatment are largely lacking.

Even the addition of the sulfanilamide compounds to the chemotherapeutic methods previously used, and in large measure discarded because of inconsistent and unsatisfactory results, has not appeared to solve the problem in its entirety. Recent studies in the field of the treatment of staphylococcemias are, therefore, of interest.

**Diagnosis**—MacNeal, Frisbee and McRae<sup>36</sup> very properly call attention to

the repeatedly positive blood culture during life is of paramount importance.

This might be considered somewhat self-evident. Strangely enough, however, blood culture technic is not infrequently inadequate in its technical details and, under these circumstances, the presence of staphylococci in broth cultures may well be misleading and the interpretation of such a finding open to serious error.

When it is remembered that the staphylococcus is a practically ubiquitous organism in the skin, hair follicles and cutaneous glands, it is obvious that only careful attention to the details of blood culture technic will avoid results capable of misinterpretation. It is quite apparent



that to diagnose staphylococcemia upon the presence of staphylococci in a broth flask inoculated with venous blood easily may be open to serious error and the lack of appreciation of this fact is, perhaps, the most common error associated with this condition.

A very pertinent paper in this connection is the report of Fox and Forrester<sup>37</sup> of a critical analysis of a large series of blood cultures in a general hospital. Despite adequate controls and careful technic, they recognize contamination with diphtheroids in 19 per cent and with skin cocci in 24 per cent of the cultures and say: "Growth in one bottle may confuse the bacteriologist, but it is much more likely to be confusing to the clinician if he is informed of it."

There are not infrequent reports in the literature of "staphylococcemia" which, in some instances, at least, seem based upon inadequate, poorly-controlled or misinterpreted bacteriological evidence. There are also instances in which staphylococcemia, diagnosed upon single positive cultures in a single broth flask, by reason of the clinical outcome, has been regarded as a relatively benign condition associated with low mortality. These, too, are diagnoses open to question, for, by all the experience of careful observers, a true staphylococcemia demonstrable by adequate and accurate bacteriological evidence, is a condition with grave implications, associated with high mortality, and presenting a therapeutic problem of no mean proportions.

Obviously, therefore, the bacteriological diagnosis of staphylococcemia must be safeguarded by carefully controlled technic, the results of which must be equally carefully evaluated.

In the presence of staphylococcemia it is of definite practical clinical significance and applicable to the evaluation of the therapy applied to report positive cul-

tures, not simply as "positive," but in terms of the number of colonies per cubic centimeter of blood.

And it is advisable that any culture positive for staphylococci be checked by a repeat culture, taken with even more meticulous care, before a diagnosis of staphylococcemia is made. This is particularly true when growth occurs in only 1 culture medium or only 1 flask or tube.

In the interpretation of blood cultures it is also important to recognize that the terms bacteriemia and septicemia are best not looked upon as synonymous. Undoubtedly, in many diseases, and under many conditions, bacteria may enter the blood stream, usually in small numbers, producing a bacteriemia in the strict bacteriologic sense. Such entry, however, is minimal and transient and the organisms are rapidly removed and destroyed. Septicemia should be used as a clinical term, implying not only the presence of bacteria in the circulating blood, but also associated clinical signs and symptoms (pyrexia, multiple localized lesions, petechial hemorrhages, etc.) indicative of systemic reaction to the invasion.

Such a diagnosis can safely be based upon a concomitant demonstration, not only of systemic signs and symptoms, but also repeatedly positive blood cultures of the same organism. Even so, the term septicemia—inherited from the past, antedating the development of bacteriology, and, in fact, not much more precise in meaning than its lay equivalent of "blood poisoning"—might well be discarded without great loss in favor of bacteriemia which, with the limitations already referred to, has, at least, a definite and precise significance.

**Treatment**—As has been above suggested, the evaluation of therapy in staphylococcemia has been obscured by

failure to establish, and apply, adequate diagnostic criteria. Much of the difficulty arises also from the inherent characteristics of the condition itself of which, perhaps, the continuous, though intermittent reinvasion of the blood stream from secondary foci, is the most outstanding.

In bacteriemia, the organisms do not continuously circulate in the blood stream, reproducing as they go. On the contrary, they are more or less rapidly removed or filtered out by the regional lymph-nodes and the tissue in general. There are thus established secondary foci from which, at irregular intervals and in varying degree, reinvasion of the blood stream occurs, each in turn capable of establishing further secondary foci.

It is this fact which renders the satisfactory treatment of staphylococemia so difficult, for the majority of such secondary foci are inaccessible to the establishment of direct drainage by surgical intervention and equally inaccessible to the direct attack of chemotherapeutic measures effective in the test-tube. Any bacteriologically lethal or inhibitory agent can only exert its effects when bacterial exposure to its action occurs in the optimum degree and such exposure is in large measure difficult, if not at times impossible, when the organisms are ensconced in secondary foci and more or less walled in by the contiguous and adjacent tissue reaction produced by their presence.

In the treatment of staphylococcemias, MacNeal and his associates have been, perhaps, among the most ardent advocates of *bacteriophage*, though it must be admitted that their enthusiasm is not generally shared.

While the majority are in accord that bacteriophage therapy is effective and useful when this agent can be directly applied to an accessible and localized

lesion, its efficiency as an intravenous therapy in the presence of staphylococemia has been the subject of continuing discussion.

As MacNeal and his associates<sup>28</sup> emphasize, it is of paramount importance that the bacteriophage must be specific for the specific bacteriological strain involved. Stock bacteriophage may be used as an *ad interim* stop gap, but a specific bacteriophage must be prepared from the original cultures at the earliest possible moment.

When prepared, the 'phage is administered intravenously through the same needle employed to secure a blood culture immediately prior to the injection of the 'phage. This is essential as a means of following the course of events by quantitative blood cultures taken before each injection of 'phage.

The initial dosage advocated by MacNeal is ordinarily 1 cc. for children and 2 cc. for adults, although when quantitative blood cultures suggest a massive invasion (50 colonies or more per cubic centimeter), this may be increased to 10 cc.

Subsequent intravenous injections are then given at approximately 45 minute intervals, increasing in amount in arithmetical progression (1, 2, 3, 4 to 10 cc.) or, in the presence of massive invasion, 5, 10, 15, 20 to 100 cc., the size of the dose and rate of increase being adjusted to the circumstances at hand.

Ordinarily, these spaced injections are continued until a reaction occurs, although they are ordinarily stopped if no reaction has occurred after the administration of 200 cc. to a child under 5 years; 400 cc. to children 5 to 12 years; and 600 cc. in adults.

The desired reaction consists of fever (occasionally even pyrexia, chill, rigor, dyspnea), followed by sweating and rapid fall of temperature.

*Oxygen, adrenalin* and *external heat* may be required to alleviate these symptoms.

After an interval of 8 to 12 hours, 'phage injections, in an amount equal to one-half the last dose preceding the shock reaction, are continued, giving 1 dose morning and evening and continued until the blood culture remains sterile for 3 to 4 days. The injections should be continued until the patient is convalescent, then once a day until out of bed, then once in 48 hours until he leaves the house, and, finally, once or twice a week for 3 to 6 months.

Under this regimen, very probably largely because of its thoroughness, MacNeal's results have been significant and warrant careful consideration.

Among the therapeutic agents applied to staphylococcemia which have fallen somewhat into disrepute is *staphylococcic antitoxin*. Relatively recently, however, observers have advanced the suggestion that the unsatisfactory results of antitoxin therapy in staphylococcemia may have been due more to inadequate methods for its use than to any inadequacy on the part of the antitoxin itself.

Among the recent workers to report upon this subject is Weiss,<sup>39</sup> who studied the antistaphylolysin titers of the blood after the therapeutic administration of staphylococcus antitoxin.

Weiss advocates much larger dosage than ordinarily used—from 100,000 to several million units, as indicated by a titer of antistaphylolysin in the serum, the objective being a concentration of 15 to 25 alpha units per cubic centimeter of serum. Antitoxin is given both by intramuscular and intravenous routes, the former being less rapidly eliminated and hence in some measure preferable.

Under this regimen he reports results deserving of study in the original paper.

## TRICHINOSIS

### Studies in Diagnosis

Rather extensive investigations within the past few years have shown that the incidence of trichinosis in the United States is somewhat greater than has hitherto been supposed.

While the diagnosis of trichinosis in the acute phase of a typical attack presents no great clinical difficulty, many cases do not present the classical picture and in these, as well as in mild attacks, the diagnosis may present some difficulty. While it is recognized that eosinophilia is one of the most easily detectable, relatively constant and definitely significant symptoms of trichinosis, it is also recognized that eosinophilia is not pathognomonic of trichinosis, but serves as a valuable indicator of this diagnostic possibility.

The demonstration of trichina larvae in the tissues or body fluid is, of course, pathognomonic. As this, however, is not always readily accomplished, attention has been directed to other avenues of laboratory investigation, particularly, since the work of Bachman and others, to the development of satisfactory precipitin and intradermal reactions.

Reports of the clinical application and value of these procedures have been somewhat variable, largely, perhaps, because of lack of standardization of antigens and technic.

The most recent report is that of McNaught, Beard and Myers,<sup>40</sup> whose results are of significance.

A trichinae *antigen* for intradermal tests is not yet commercially available; it must be prepared. The method advocated by these workers is, briefly, as follows:

Adult white rats infected with larvae are killed after 5 weeks, eviscerated, skinned and ground in a meat chopper. The tissue is then digested in an aqueous solution of 1 per cent

pepsin, and 0.7 per cent HCl for 6 to 12 hours in a 37.5° C incubator, using about 1 liter of this solution to each 100 grams of tissue, the mixture being agitated from time to time. The digest is then sieved (60 mesh) and placed in large funnels fitted with a rubber tube and pinch-cock. The larvae settle rapidly and are drawn off into round glass jars (200 cc capacity) covered with 4 layers of cheesecloth fastened by a rubber band, the jars then inverted over conical sedimentation glasses filled with tap-water and placed in the incubator.

After a few hours the motile larvae pass through the cloth, leaving the debris behind, and settle to the bottom of the sedimentation glass. The larvae are then transferred to a 50 cc. conical centrifuge tube and washed in tap-water until clear. Any small amount of debris carried is easily removed with a capillary pipette. After removal of excess water, the tube is rotated in a carbon-dioxide or salt-ice bath until the contents are frozen solid over the inside of the tube. The tube of frozen larvae is then placed in a vacuum desiccator containing calcium chloride and dry NaOH, evacuated with a high vacuum pump for 30 minutes and then sealed. After about 18 hours the thoroughly dried flaky mass is removed, placed in glass vials and weighed amounts, and sealed for future use.

For precipitin tests a weighed amount of dried larvae, as above prepared, is extracted with a buffered saline solution in amount sufficient to make a 1:100 concentration. This solution contains NaCl 0.5 per cent;  $\text{Na}_2\text{HPO}_4$  0.143 per cent;  $\text{KH}_2\text{PO}_4$  0.036 per cent; and 0.4 per cent phenol at pH 7.1. After 12 to 18 hours in the refrigerator, the suspension is placed in a ball mill (250 cc. centrifuge flask half-full of 5 mm. steel balls) and slowly revolved horizontally overnight.

The turbid solution resulting is used 1:100 for precipitin tests and 1:500 and 1:10,000 for intradermal tests, these latter dilutions being made with the buffered saline solution already described.

The latter solutions, tested for sterility, are stored in 2 cc. ampoules fitted with a rubber cap such as is used for vaccine bottles.

The *intradermal tests* are performed by injecting 0.1 cc. of 1:10,000 extract with a tuberculin syringe as usual.

A wheal 7 mm. or more in diameter together with an erythematous zone up

to 20 mm. and definitely larger than the control, is considered a positive reaction.

It is emphasized that this reaction may reach its maximum in 20 minutes and disappear by the end of 1 hour. Frequent or even continuous observation thus is necessary.

The *precipitin test* is performed by carefully layering 0.2 cc. of 1:100 dilution of antigen over 0.2 cc. of clear un-inactivated serum in a thin walled, 7 mm. serological test-tube. A control consists of layered buffered saline. After 1 hour in the 37.5° C. water bath a whitish 1 mm. ring at the junction of antigen and serum constitutes a positive reaction. Chylous or hemolyzed sera are not satisfactory for precipitin tests.

After the first reading of the tests, the tubes are mixed by agitation and again read after 12 to 24 hours at room or refrigerator temperatures. A positive reaction now shows a heavy flocculent sediment whirling upwards when the tube is tapped with the finger.

Using these methods, the following series were studied:

Of 36 cases showing classical symptoms of trichinosis, 97.2 per cent (all but 1) eventually gave immediate skin reactions. The negative reaction occurred in a moribund patient.

Of 36 cases in which trichinosis was a diagnostic possibility, 17.2 per cent gave a positive skin test.

Of 194 controls, 6.7 per cent gave an immediate positive and 18.1 per cent a delayed type of skin reaction.

Precipitin tests were in almost perfect agreement.

By a *delayed skin reaction*, these authors mean a reaction reaching its height in about 24 hours. The initial discoloration forms no wheal and fades but is succeeded by a gradually developing, slightly swollen, tender, reddened area 1 to 3 cm. in diameter, resembling a

mild tuberculin reaction, reaching its maximum in 20 to 24 hours and then slowly subsiding

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## DERMATOLOGY

By JOHN B LUDY, A B, M D

## Acne Vulgaris

**Treatment**—Since the therapeutic results in the treatment of acne vulgaris are so mediocre, Lynch<sup>1</sup> has suggested the use of *nicotinic acid*. It was given to 46 university students who had had no previous treatment for acne or no treatment for at least 3 months preceding trial of this drug. The nicotinic acid was administered twice daily in the form of 5/6 grain (50-mg) tablets taken after the morning and evening meals. No other treatment

was used, and the students were given no advice as to diet or hygiene.

The only unpleasant reaction observed in this group of patients was transitory redness, burning or itching in the flush areas of the face, chest and arms. This reaction usually could be avoided by taking the drug immediately after meals.

Eight of the 46 patients failed to present themselves for re-examination. The remaining 38 patients were examined at 3 or 4 weeks and again at 6 to 8 weeks. In

6 (16 per cent) the results were classed as good and in 15 (39 per cent) as fair, in 17 (45 per cent) no improvement was noted.

The improvement observed in 55 per cent of patients with acne is not particularly encouraging when it is realized that the disease is cyclic and self-limited, so that in any series of patients with acne, whether treated or not, a considerable number will show improvement. The results in certain cases were so satisfactory, however, that this report was considered justifiable. Nicotinic acid cannot be regarded as a cure for acne, nor is it responsible for all the improvement noted in these patients, but it is a simple and apparently harmless drug which appears to be helpful.

Lynch is unable to explain the mode of action of nicotinic acid, but it may be noted that it is one of the factors in liver, which has been repeatedly advocated in the treatment of acne, and there is some relation between nicotinic acid and the metabolic requirements of the staphylococcus. In a few patients the influence on the seborrheic oiliness of the face was most striking.

### Bismuth Therapy

**Effect on Latent Plumbism**—In discussing the effect of bismuth therapy on latent plumbism, Epstein<sup>2</sup> states that in comparison with the arsenicals and mercurials employed in the treatment of syphilis, the bismuth preparations show a notably low toxicity. Stomatitis constitutes the only commonly encountered complication following the intramuscular injection of bismuth salts. Other reactions, including arterial and venous embolism, abscesses, arthralgia, jaundice, nephritis and cutaneous lesions, are rarely seen.

Stokes listed such disturbances as abdominal cramps, diarrhea, polyneuritis,

psychic symptoms and erythropoietic disturbances as following the administration of bismuth in the treatment of syphilis. These are also regularly noted in lead poisoning. This communication suggests that some of these reactions reported as being due to bismuth may actually have been the result of lead toxicity. Bismuth and lead are closely related chemical elements, and there is no reason why the toxicology of one should not resemble the toxicology of the other to a certain extent. Latent plumbism is commonly encountered, however, especially in industrial centers, while bismuth toxemia is comparatively uncommon. Case reports show that latent plumbism may become active after the injection of bismuth as an antisyphilitic agent.

Antisyphilitic therapy must be as nearly reactionless as possible to be successful.

It has been proved amply that lead is stored in the skeletal system of the body. In this location it is believed to be innocuous. When the stored metal is mobilized, however, *i. e.*, when it is removed from the bones and taken into the circulation, a characteristic group of symptoms appear. This, of course, occurs when the amount of lead in the blood exceeds the concentration that the body can tolerate. These symptoms include pigmentation near the gingival margin, abdominal cramps, constipation or diarrhea, peripheral neuritis, anemia, stippling of the erythrocytes, encephalopathies and other derangements.

This mobilization may be accomplished in many ways. As simple a factor as an acid diet may be all that is necessary. Roentgenographic studies have shown that a lead line may be demonstrated near the epiphyses of growing children suffering from lead poisoning. A similar line has been found after bismuth therapy, and the consensus is that these lines are radio-

logically indistinguishable. This suggests that the 2 metals are stored in the same location. Fishback and Fishback have demonstrated that after antisyphilitic therapy the greatest amount of mobile bismuth is found in the bones.

It is possible that the deposition of bismuth in the osseous system leads to the excretion of lead and explains the development of signs and symptoms of lead poisoning in such patients. These manifestations are dependent on the amount of lead in the circulation and not on the total amount present within the body.

A survey of the occupations in which the worker is exposed to lead suggests that latent plumbism must be common. According to Solis-Cohen and Githens, the exposed workers include painters, lead miners, lead workers, plumbers, typesetters, dye workers, storage battery builders or repairers, enamelers, bullet makers, pottery glazers, paint manufacturers, solder handlers and gasoline (tetra-ethyl lead) handlers. Under these circumstances it is not surprising that bismuth therapy should occasionally cause activation of latent lead poisoning if the mechanisms suggested in this communication are correct.

**Summary**—The cases of a painter and a smelter worker are reported. Signs and symptoms of lead poisoning in both patients followed the administration of bismuth in the treatment of a syphilitic infection.

It is suggested that bismuth may replace the lead stored in the bones and lead to the mobilization of lead, with the development of such symptoms as cramps and a lead line.

Prophylactic treatment of lead poisoning in those exposed to the influence of the metal may decrease the incidence of untoward reactions following bismuth therapy.

### **Dermatophytosis Pedis**

**Treatment with Medicated Insoles**—In discussing the incidence and treatment, Seldowitz<sup>3</sup> states that in recent years dermatophytosis pedis has been receiving major consideration because of its rapid and universal spread and frequent resistance to prophylaxis and treatment. Morginson estimated that 10 per cent of all cutaneous infections treated today are due to fungi. He stated that in a recent survey at the University of Pennsylvania 59.7 per cent of 1073 students examined were found to be infected. Legge, Bonar and Templeton conducted a similar survey at the University of California and found that of 1000 freshmen entering the university, 51.5 per cent were infected; at the end of the first semester this number was increased to 78.6 per cent.

A review of the literature on the treatment of dermatophytosis pedis reveals a variety of therapeutic procedures, with many variables in the results obtained. In their study conducted at the University of California over many years, Legge, Bonar and Templeton attempted to establish the efficacy of a number of therapeutic agents, which included 30 per cent sulfurous acid in glycerin, 1 per cent thymol in glycerin, Castellani's solution, a 10 per cent ointment of benzyl peroxide, tincture of iodine and glycerin in equal parts, a 10 per cent solution of sodium thiosulfate, compound ointment of benzoic acid N. F. with 1.5 per cent thymol, 4 per cent chrysarobin in chloroform, a pine oil soap solution, 5 per cent gentian violet in alcohol, 5 per cent aqueous solution of mercurochrome, 10 per cent ointment of copper oleate and ultraviolet irradiation from a quartz mercury vapor glow lamp with a special applicator. The best results were obtained with *compound ointment of benzoic acid N. F.*

containing 1.5 per cent *thymol*. Complete recovery was obtained in 29 per cent of patients thus treated, and another 35 per cent showed at least 50 per cent clinical improvement, giving what the authors termed satisfactory results in 64 per cent of the patients treated by that agent. Six per cent of the patients showed definite evidence of irritation. The highest percentage of cures was obtained with *tincture of iodine and glycerin*. They obtained recovery in 31.7 per cent of patients treated with this agent and satisfactory improvement in another 24.6 per cent. About 2 per cent showed evidence of irritation.

The treatment of dermatophytosis of the feet should be based on a comprehensive knowledge of the many problems arising in this type of infection. It has been established that the causative fungi frequently lead a prolonged and hardy life, with a resting spore age of indefinite duration and latent virulency. Parkhurst stated that its spores can survive as long as 25 years on glassware. The fungus, with its predilection for the interdigital spaces, causes local irritation and inflammation, maceration of the skin and increased perspiration. Frequently an objectionable odor accompanies the infection, due to the putrefaction of the excessive perspiration and to the macerated epidermis. Because of the nature of the causative fungus, treatment necessarily must be constant and prolonged. The employment of strong antiseptics is contraindicated, as a rule, because frequently they have no effect on the mycelia and often produce local injury to the skin. Souter and others advocated an ideal, hypothetic therapeutic agent which should possess the following characteristics: (1) ease of application, (2) fungicidal or at least fungistatic action, (3) the ability to penetrate to the fungus in normal or pathologically altered

structure of the epidermis, (4) nonirritation of the skin, (5) the ability to lessen perspiration and to prevent its putrefaction, and (6) the ability to deodorize.

**Fungistatic Effects of Medicated Insoles.** Recently Kahn and Carroll have demonstrated that rubber containing 8-hydroxyquinoline was bacteriostatic for many organisms, particularly the staphylococcus. Seldowitz has demonstrated the practical application of this finding in the treatment of impetigo contagiosa. On further experimentation Carroll and his co-workers found that the addition of parachlorometaxyleneol and chlorthymol to the rubber base combination imparted definite fungistatic properties to this substance. A method was then devised to render an ordinary leather insole fungistatic. The air in the pores of the leather was evacuated and replaced with rubber. This rubber was then impregnated with *8-hydroxyquinoline, parachlorometaxyleneol* and *chlorthymol*.

**Technic.** The method of application of the insole was simple. The patient was instructed to insert the treated insole into his shoes and to wear his socks and shoes in the regular manner. Each patient continued his daily routine without interference. When the infection was extensive and the lesions extended on the dorsal surface of the foot, the insole was augmented with a rubber moccasin. This moccasin contained the same chemical ingredients as the insole and was worn over a pair of socks only at night. Only a few isolated patients required the use of these moccasins. In the control group of cases an untreated insole was substituted for the leather-chemical compound. In some instances the control period had to be short because of the rapid spread of the infection. The patients were examined at intervals of 2 weeks, and the clinical progress was



noted. Records were kept as to the physical appearance of the lesions, such as scaling, fissuring, vesicle formation, degree of inflammation and denudation, as well as of the subjective symptoms, such as pruritus, perspiration and odor.

This survey was limited to 125 patients and many interesting observations were recorded. It was noted that the younger the patient and the more recent the infection, the more quickly amenable was the infection to treatment. None of the patients wearing the medicated insoles complained of any discomfort during the period of therapy; however, 2 patients experienced a slight tingling or burning sensation with the wearing of the medicated rubber moc-casins.

**Summary**—A new and simple method of treatment for dermatophytosis pedis is described.

The fungistatic action of leather insoles containing rubber impregnated with 8-hydroxyquinoline, parachlorometaxylenol and chlorthymol against *T. interdigitale* is demonstrated.

Of 40 treated patients with positive cultures and mycelia demonstrable on direct microscopic examination, in 29, or 72.5 per cent, the condition was clinically and mycologically cleared in an average period of 4 months.

Of 19 treated patients with negative cultures but with mycelia demonstrable on direct microscopic examination, in 15, or 80 per cent, the condition was clinically and mycologically cleared in an average period of 2½ months.

Of 51 treated patients with negative cultures and no microscopic findings, the condition was cleared in an average period of 2 months.

The employment of medicated insoles as a prophylactic measure against dermatophytosis pedis is a reasonable deduction.

## Gentian Violet in Skin Disorders

Gentian violet possesses a high potency against certain bacteria and fungi. It has an extremely low toxicity for tissues, and is one of the most valuable topical agents available for the treatment of a number of superficial infections of the skin, according to Thomas.<sup>4</sup> Its antiseptic-coagulant properties should render it of particular use in war therapy, both for the prophylaxis and treatment of superficial *war wounds* and for *burns*. Its obvious disadvantage is the temporary staining of the patient, and his clothing or bed-linen, a deep purple color.

Gentian violet is a basic dye of the triphenylamine (rosaniline) group. It occurs as a greenish crystalline substance, and is soluble in water, alcohol and chloroform. It is insoluble in ether. For local application it is generally used in a 1 or 2 per cent aqueous solution. At this strength it is practically non-irritant and nontoxic. Idiosyncrasy to it is rare, and it therefore can be applied safely, if necessary, in or around the mouth or to babies' skins, and no ill-effects are likely to result from absorption when large areas are painted with the dye. Alcoholic solutions are best avoided, as they are liable to produce a local reaction from the irritant effect of the alcohol.

**Pyogenic Skin Infections**—In these infections the dye kills or inhibits the growth of most gram-positive micro-organisms, being particularly active against staphylococci. Among the many staphylococcal and streptococcal skin infections which yield to it are *impetigo*, *infective dermatitis*, *suppurative folliculitis* and *perifolliculitis*, and *paronychia*; it may also be effective in dermatoses which have become infected secondarily, such as *eczema* or *dermatitis*, *ringworm*, *pediculosis*, and *scabies*, provided, of course,

that the primary cause (as in pediculosis and scabies) has first been specifically dealt with. In the commonly seen *infective dermatitis of the face*, for example, the gentian violet is a useful alternative to the copper and zinc sulfate lotion known as *eau d'Alibour*. Both these agents are antiseptic-coagulants and are much superior to the greasy applications, such as ammoniated mercury ointment, which are so often employed in this condition and which undoubtedly tend to irritate the sensitive epidermis and to spread the infection. If the *scalp* is affected, especially in a child, it is important to search for pediculi; a discharging ear is another common primary cause of infective dermatitis of the face.

Gentian violet can be very helpful in more deeply seated staphylococcal infections involving the pilosebaceous apparatus, such as ordinary *furunculosis*, *Bockhart's impetigo*, *occupational oil acne*, etc. These conditions are spread mainly by auto-inoculation, which can often be prevented if the whole of the affected area is painted with the dye and not merely the individual lesions. A pustular folliculitis of similar type may complicate *eczema*, sometimes occurring as a result of prolonged use of tar-containing ointments, or it may be superimposed on a simple dermatitis, such as the napkin variety in small babies. In the treatment of *secondarily infected dermatoses* of this kind the applications of *gentian violet* may often be advantageously supplemented by *wet dressings of an aqueous solution of mercury perchloride* (1:4000), which help the dye to penetrate deeper, while tending to destroy other organisms which may be present and not amenable to the gentian. In *staphylococcal paronychia* gentian violet is well worth trying, and should be introduced underneath the posterior nail-folds once or twice daily in a 3 per cent

aqueous solution on the sharpened end of an orange-stick. It must be remembered that, whatever local remedy is used, a necessary part of the treatment of this troublesome complaint is to **keep the hands out of water**. The condition is frequently of occupational origin; persons whose hands are constantly wet are the most liable to be affected, i.e., cooks, barmaids, dish-washers, and the like.

In fungus infections dyes do not, as a rule, possess such powerful fungicidal as bactericidal properties. Gentian violet, however, often may be employed usefully in the common *ringworm of the feet or groins*, especially if secondarily infected, but it is against certain yeast-like fungi of the monilia group that it is particularly active. The most important member of this family is *Oidium albicans*, which is, of course, the cause of the familiar coagulated milk like infection of the mouth seen generally in babies or in elderly debilitated subjects, and called *thrush*. *Oidium albicans* and its relatives may also attack other parts of the cutaneous surface and mucous membrane. Warmth and moisture foster the growth of these organisms, so that they are particularly liable to flourish in areas such as the genito-crural and intergluteal folds, and between the toes and fingers. A monilial infection may be the cause of *napkin eruption* in small babies, usually involving the genito-crural furrow itself and not merely the contiguous skin surfaces, as in simple napkin dermatitis. Thrush-infected skin may present a sodden macerated appearance with surrounding inflammatory reaction and sometimes blister formation. It may be indistinguishable clinically from ringworm.

*Anal and vulval pruritus* may be the result of a monilial infection; vulvovaginitis, due to this infection in partic-

ular, may set up a most intractable irritation and is often complicated by superadded vulval dermatitis due to a combination of rubbing and drastic local medication. In a study of 200 pregnant women attending a leukorrhea clinic, Liston and Cruickshank<sup>5</sup> found that thrush was the cause in 49 cases, an incidence of approximately 25 per cent. These workers also draw attention to the favorable influence of glucose on the development of thrush, and to the fact that diabetic vulvitis can frequently be attributed to thrush infection fostered by the glycosuria and not to any direct irritant action of the diabetic urine. Oidium can cause the pearly, wrinkled lesions at the corners of the mouth in children, known as *perlèche*; here, again, the same favorable conditions for the fungus are found, *i. e.*, warmth, moisture, and 2 contiguous surfaces. As already mentioned, oidium may set up a paronychia which, like staphylococcal paronychia, is liable to occur in persons doing wet work or handling sugar—confectioners, for instance.

The treatment of *burns* is of particular importance at the present time. In modern warfare burns may be produced by a number of agents, both physical and chemical. Mitchiner<sup>6</sup> considers that gentian violet is probably the most valuable local application for all these burns, both as an emergency measure and in hospital treatment. Immediate coagulation of the burned area is essential in order to prevent early collapse from loss of fluid and absorption of toxins; gentian violet fulfills these requirements, as it is an excellent antiseptic-coagulant. It has, moreover, an analgesic effect which is important, as pain is another cause of early collapse in burns. A further recommendation is its virtual lack of irritating properties and toxicity; the extensive use of an agent such as picric acid,

for example, would certainly result in a large number of cases of eczematous and blistering dermatitis from intolerance.

Gentian violet is best applied as a compress dressing of lint or gauze, 3 or 4 layers thick, which should be soaked in the solution and laid over the entire burned area. In chemical burns neutralization of the burning agent is, of course, necessary before coagulation is attempted. Hospital treatment involves thorough surgical cleansing of the burn, whether or not an emergency coagulant has been used. After such cleansing, the hospital dressing of superficial burns is again a question of an efficient antiseptic-coagulant, and for this purpose Mitchiner states that under war conditions the most satisfactory is a 1 per cent aqueous solution of gentian violet. He advises that the compress should be left alone (except for inspection), unless a rise of temperature or pulse indicates sepsis. The coagulum will separate from the burnt area in 10 to 14 days, and can be lifted away painlessly and easily when it is ready.

**Ulcerative Reaction in Treatment of Impetigo Contagiosa**—Permanent scarring following uncomplicated impetigo contagiosa is rare. With the use of the occlusive method of treatment of impetigo with such agents as adhesive plaster or the less effective collodion, no deep extension of the lesion to an ecthymatiform ulcer has been observed. With the crusting type of therapy no such ulcerations have been seen with silver nitrate, cupric sulfate or tannic acid-mercury preparations.

With the gentian violet crusting method, however, this reaction has occurred occasionally in the past 2 years, as observed by Goldman.<sup>7</sup> It has been seen in 4 cases, in 2 infants and 2 adults. In these cases a smooth gentian violet

crust formed over the impetigo areas. Instead of curling up, shrinking and peeling off, as the usual gentian violet crust does, the crusts in these instances remained fixed firmly to the skin for a relatively long period, *i. e.*, more than 2 weeks and in 1 case 5 weeks. The skin adjacent to the adherent crust showed no redness, tenderness or edema. When the crust was removed, however, either with wet dressings or with scissors and forceps, a deeply punched-out area filled with pus was found. With irrigation and application of mercury ointments these areas healed rather rapidly but left ugly punched-out scars, some resembling a postvaricella scar and others the depressed scar of an ecthymatous ulcer. These were seen chiefly on the face and, in 1 infant, deep in the axilla. There was no evidence of hypersensitivity to gentian violet in any of the cases.

In 3 cases a saturated alcoholic solution, containing approximately 30 per cent gentian violet, was used. In 1 case, that of an adult, there were small depressed scars following impetigo spots treated with a 1 per cent aqueous solution of gentian violet; other lesions on the patient's face, treated with 5 per cent ammoniated mercury ointment, showed no scars. The saturated alcoholic solution of gentian violet was used because of its excellent results in cases of impetigo of Bockhart and of pustular miliaria. Originally, it seemed to be desirable in impetigo contagiosa, in spite of the transient pain, because a firm heavy dry crust forms over the entire lesion in a few seconds to a few minutes, whereas the impetigo lesion treated with repeated applications of an aqueous solution of gentian violet continues to ooze for several hours. No bacteriologic studies were made of the material under the gentian violet crust.

In the gentian violet therapy of *burns*, failure of healing under the firm gentian violet crust has been observed.

This complication of the gentian violet treatment of impetigo contagiosa must be uncommon when the popularity of this method is considered. From the small group of cases observed, the saturated alcoholic solution of gentian violet is much more apt to cause this. The complication should be suspected when there is no evidence of separation of a gentian violet crust after an arbitrary period of approximately 2 weeks.

### Milkers' Nodes

Nodular, inflammatory lesions, which are infectious and transmittable from man to man, have been observed on the hands of milkers (Fig. 1). It commonly occurs in Europe and 4 cases have been reported in America by Becker.<sup>8</sup>

The microscopic examinations of these 4 cases were similar to those described in the literature and the essential features may be summarized as follows:

There was considerable increase in the stratum corneum with hyperkeratosis and parakeratosis (Fig. 2). Acanthosis and spongiosis were present and in the upper layers of the rete malpighii there were an increased intracellular edema which produced in some scattered areas enlarged clear cells with only a thin cellular membrane and in other areas there were microscopic multilocular vesicles. The dermis was edematous with an increased vascularity (Fig. 3) and dense cellular infiltration was present which disrupted the epidermal-dermal junction. This infiltrate was made up principally of lymphocytes and also many plasma-cells, eosinophiles and an occasional giant-cell and polymorphonuclear leukocyte. The increased intracellular edema with the formation of micro-

scopic multilocular vesicles could be interpreted as a mild degree of reticular degeneration as described by Unna. In none of the microscopic sections studied was there any evidence of pustulation.

It is quite evident, both clinically and histologically, that the lesions occurring in the 4 cases described are similar in nature to those recorded in the German literature as "*melkerknöten*." All individuals afflicted had been engaged in milk-

to show any definite relation between the 2 disorders were Schultze, Seifried and Schaaf. Paschen and Groth, however, believed that these cases were vaccinia and not true milkers' nodules. Experimental work of Stark and his co-workers support the theory that the organism of milkers' nodules was of decreased virulence because only after repeated transfers to the same species of animals were they able to show conclusive evi-



Fig 1—Case 2. Typical milkers' nodule with 2 secondary lesions. Photographed by Dr. R. H Puumala. (Becker: Jour Am Med Assoc)

ing cows on whose udders open ulcers or crusted lesions had been present. The cause of milkers' nodules is undoubtedly infectious, because the condition is self-limited, healing spontaneously without treatment and apparently leaving an immunity to further similar inoculations. The writer's inability to demonstrate any bacteria both by culture and by animal inoculation, plus the fact that many investigators have found inclusion bodies in a microscopic section, would indicate that the infecting agent is a filtrable virus.

The relation of this virus to vaccinia is still in a controversial state. The first

dence that the virus had the characteristics of variola vaccine.

It is generally agreed that for a virus to be similar to that of variola a positive *Paul test* must be obtained and the individual infected should acquire an immunity against vaccine virus. The majority of investigators of milkers' nodules have been unable to obtain positive Paul reactions from their cases and most of their patients have not acquired any immunity to smallpox vaccine. The writer's results of a negative Paul test in 2 of the cases and a lack of immunity to vaccination as demonstrated in 2 others agrees with most investigators. Because



Fig. 2—Low power magnification of section from Case 2 showing hyperkeratosis, multilocular vesicles and dense cellular infiltrate in dermis; stained with hematoxylin-eosin. (Becker Jour. Am Med Assoc.)

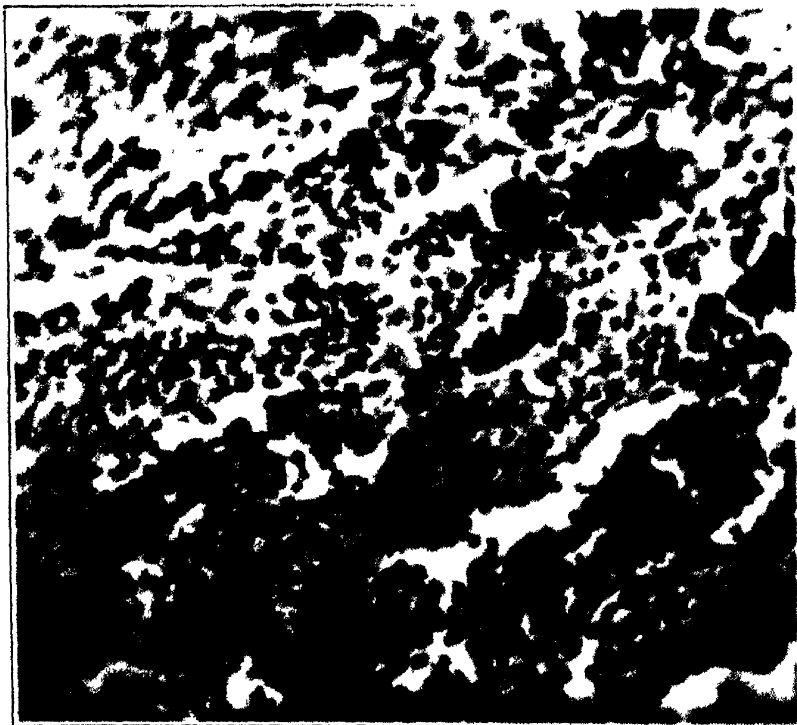


Fig. 3—High power reproduction of Fig. 2, showing the dermis with dense multicellular infiltrate and marked blood vessel dilatation. (Becker: Jour. Am. Med. Assoc.)

of these 2 facts, therefore, along with the difference in histologic picture and in the clinical course of milkers' nodules, there does not seem to be much evidence to support any relation to variola vaccine. On the other hand, the pathologic process of milkers' nodules seems to show a close similarity to *paravaccinia*, as neither of the disorders produces immunity to subsequent inoculation with vaccine virus, as the Paul test is negative and the microscopic appearances are similar in the 2 instances.

**Summary** — No relation between milkers' nodules and vaccinia could be demonstrated in these cases, as the Paul test, which was performed with material from 2 cases, was negative and 2 of the infected persons showed no immunity to smallpox vaccination.

The clinical course of milkers' nodules and the distinct variations in the pathologic picture are further evidences that this disease shows no relation to variola vaccine.

The cause of milkers' nodules is apparently a virus which may be either an attenuated or biologic modification of vaccine virus. From all evidence, it more closely resembles the paravaccine of Lipschutz.

The writer believes that milkers' nodules are not rare in this country and that many doctors in dairy communities must have seen these cases. Calling attention to the disease should bring forth many new case reports.

### Sulfanilamide

**Excretion Through the Skin**—In recent years there has been an increasingly important rôle attributed to streptococci acting on the surface of the skin. Because some streptococci have been shown to be peculiarly vulnerable to sulfanilamide in other parts of the body,

Cornbleet<sup>9</sup> considers it timely to consider and investigate the excretion of this substance through the skin.

The literature on sulfanilamide has become extraordinarily voluminous in the short time that the product has been available. That part of the literature which has concerned itself with storage has been relatively meager. Pinto<sup>10</sup> determined the excretion of sulfanilamide in *human milk*. He observed that the concentration of the drug in the milk follows that in the blood. The peak of the curve in the milk lags several hours behind that in the blood. He further observed that more than one-half the sulfanilamide was excreted by the kidneys in the first 24 hours. Stewart and Pratt<sup>11</sup> also investigated the excretion of sulfanilamide in human milk. They stated that mothers receiving 30 grains (2 Gm.) a day had a blood and a milk level of 2 to 4 mg. per 100 cc. Women excreting about 400 cc. of milk daily excreted 8 to 16 mg. of sulfanilamide. The concentration of the drug fell rapidly in both the blood and the milk as soon as administration of the drug was discontinued. Hepburn, Paxson and Rogers<sup>12</sup> noted that sulfanilamide was still present in human milk to the extent of 0.2 to 0.3 mg. per 100 cc. 72 hours after the medication was stopped. Adair, Hesselstine and Hac<sup>13</sup> showed that 60 to 75 per cent of the drug can be accounted for in the *urine* and that little or none of it was present in the urine after 48 hours. Scudi<sup>14</sup> reported that urinary elimination of sulfanilamide was completed in 2 or 3 days. Hac, Adair and Hesselstine<sup>15</sup> made an effort to determine whether prolonged use of sulfanilamide resulted in an accumulation of the drug in *breast milk*. They gave from 30 to 75 grains (2 to 5 Gm.) of the drug to normal lactating women in 6 doses daily for 3 days during the first 9 days of the

post-partum period and noted that the level of the drug in the milk was considerably higher than that in the blood. It was still being excreted in the milk in measurable but negligible amounts 48 hours after its administration had been discontinued. The percentage of sulfanilamide excreted in a conjugated acetyl form was relatively low the first day the drug was administered, but it increased slightly the second and third days and rose sharply the fourth and fifth days, when administration of the drug had been discontinued.

Marshall, Emerson and Cutting studied the distribution of sulfanilamide in the organism. They fed the drug to dogs and several hours later bled the animals to death and analyzed the tissues. They observed that about one-fifth of the sulfanilamide remaining in the tissues was accounted for by material in the *skin*. They showed that a single large dose developed a peak concentration in the blood in 2 to 4 hours and that at the end of 24 hours the drug had usually disappeared from the blood. On the other hand, when the quantity of drug was given in daily divided doses, 2 to 3 days were necessary to establish an equilibrium between the amount ingested and the amount excreted. After equilibrium was established, about the same time was necessary to free the subject of the drug.

Lucas<sup>16</sup> determined the response of human beings to single doses of sulfanilamide. According to his results, the maximum concentration in the *blood* appeared in 2 to 4 hours, and the larger the dose given, the earlier the peak appeared. The maximum was not directly proportional to the dose. In several hours the concentration fell to about 2 mg. per 100 cc, and in 24 hours, to 0.4 to 8 mg. per 100 cc. Sixty per cent of the drug was excreted within 24 hours and 90 per cent within 48 hours. Traces of

sulfanilamide, mostly in conjugated form, were still present in the *urine* 72 hours after a dose of 30 grains (2 Gm.) and 100 hours after a dose of 45 grains (3 Gm.).

Higman<sup>17</sup> made observations on the excretion of sulfanilamide in *sweat*. He extracted the underclothing of a patient who was taking sulfanilamide during warm weather. He found, by a qualitative test, that this extract contained the drug. He did not make any quantitative observations. Blauch<sup>18</sup> put his subjects in a sweat bath 2 to 3 days after the last dose of sulfanilamide. He was able by means of this procedure to detect the drug again in the *blood*, *urine* and *sweat* after its initial disappearance. The sweat baths apparently mobilized drug from depots. By this method he found traces in the urine up to 7 days after the last dose. He also observed that the excretory rate was related to the volume of urine and recommended, therefore, that plenty of fluids be given when rapid elimination of the drug is desired. His figures show higher concentrations of the drug than were reported by other authors. This undoubtedly is accounted for by the method of his determinations. Maher gave rabbits daily overdoses of sulfanilamide with a stomach tube and after the animals died determined the amount of sulfanilamide in the various tissues. He found that the skin contained a large share of the entire amount in the various tissues. On the basis of extensive data derived from experiments on animals carried out with various approaches, he stated the belief that the drug was carried to all parts of the body and that there was no apparent tendency for the tissues to store or accumulate it. The tissues with the best supply of blood in general contained the largest amounts. The drug was rapidly eliminated, as shown by analysis of the tissues after



the administration was suspended for 3 days.

Carryer and Ivy<sup>19</sup> found that sulfanilamide was excreted in the *bile*, *pancreatic juice*, *gastric juice*, *succus entericus* and *saliva* of the dog in appreciable quantities. Bacteriostatic levels (from 8 to 12 mg. per 100 cc.) may be attained in the hepatic bile. Sulfanilamide appears in the bile with blood levels as low as 1.3 mg. per 100 cc. In their experiments they found that the highest concentration of sulfanilamide occurred in the gastric juice.

Almost every tissue or fluid of the body has been shown to be readily permeable to sulfanilamide. The substance finds its way into the *sweat* almost at once, just as it does into the other secretions. Only 15 minutes after the ingestion of moderate doses of the drug appreciable quantities appear in the sweat. As the sweat dries on the surface of the skin, the drug becomes concentrated. To what extent accumulation occurs in this manner it is impossible to say. An unknown factor is the rate at which the sulfanilamide is disintegrated at the surface. Still another unknown is the rate at which the drug is removed by the exfoliation of the surface epidermis. Part of the drug clings to the exfoliated material, as shown by the fact that the unfiltered sweat contains more sulfanilamide than the filtered portions. It may be that conjugated sulfanilamide is attached to the epidermis and is the part filtered out. It would be interesting to determine whether this is actually so. At any rate, it is undoubtedly true that the final concentration of sulfanilamide at the surface of the skin is higher than that in the blood when therapeutic doses are given. High enough concentrations would not be available for the organisms causing impetigo and ecthyma. They would be available, however, for the

superficial streptococci of the ears, the scalp and the cutaneous folds. Some may question the use, for such benign disorders, of a drug capable of a number of untoward reactions. The reasons would apply with even greater force with sulfanilamide to be used as a prophylactic agent against the appearance of new furuncles in furunculosis.

From the data accumulated here, the peak of the curve of concentration of sulfanilamide in the *sweat* shows a slight lag behind that of the *blood*. On this account, when administration of the drug is discontinued, the sweat contains relatively larger amounts than the blood during the phase when the quantity in the latter is receding. The amount present in the sweat at any single time, however, is definitely related to that in the blood.

Several investigators did not find any evidence of storage or accumulation depots in the body. One bit of evidence points positively in this direction: Blaich<sup>18</sup> noted that after a certain period which followed the discontinuance of the administration of sulfanilamide and in which the drug no longer could be detected in the blood and urine, it again reappeared in appreciable quantities after a sweat bath. In the experiments reported here, Blaich's observations could be qualitatively confirmed in 2 cases. In 8 instances in which the procedure followed in the confirmatory cases was exactly duplicated, the blood and urine did not again show sulfanilamide after a sweat bath.

In the present observations, too, on the skin and blood of dogs there is no evidence that sulfanilamide accumulates in the tissues. The peak of concentration and the rate of exhaustion in the *blood* and *skin* run parallel. If anything, the blood showed a trace of drug still present after traces in the skin had disappeared.

In unpublished work it was shown that as sweating proceeds, chlorides appear in increasing concentration in the *sweat* up to a certain point. This does not appear to be true with sulfanilamide. During the decrease in the concentration of the drug in sweat, the quantity of sweat secreted per units of time increases. The sweat glands evidently become more permeable to water and to some salts as they continue to function under the stimulus of heat, but other materials are allowed through at a more constant rate. To the latter group sulfanilamide evidently belongs.

Sulfanilamide continues to appear in the *milk* for a considerable period after it disappears from the blood, in contrast to the rapidity with which the drug leaves the sweat after not being found in the blood. This points to the possibility that the sulfanilamide in sweat is a filtration product. The cells lining the acini of the mammary glands become ingredients of the milk. The sulfanilamide thrown into the milk with the disintegration of these cells is apt to have been deposited in the latter an appreciable period earlier. This earlier period was one during which the blood level of sulfanilamide was higher. This is a possible explanation of the lingering presence of the drug in milk. Since the mammary glands are modified apocrine sweat glands, it would be of interest to know whether the latter follow the curve pattern of long excretion characteristic of the mammary glands or the shorter one of the eccrine sweat glands.

An experiment is reported in which the partition and storage of the drug in the blood and skin of the dog were determined.

Several experiments are detailed in which the concentration and persistence of sulfanilamide in the blood, unfiltered

sweat and filtered sweat were determined.

In some cases a sweat bath may cause the reappearance of sulfanilamide in the blood stream even several days after the drug has disappeared from it.

Shortly after the administration of sulfanilamide it appears in the *skin*. The quantity deposited there accounts for a large share of the entire amount present in the body. Sulfanilamide may be of value, therefore, for certain kinds of infections within the skin.

Through the medium of sweat, sulfanilamide is rapidly made available at the surface of the skin. There is some clinical evidence, and more may be expected in the future, to show that sulfanilamide is of benefit for the "*streptococoids*," or *superficial streptococcic infections* of the skin and its folds.

Untoward reactions from sulfanilamide occur with sufficient frequency to withhold its use in the treatment of the simpler infections of the skin that respond to less dangerous applications and drugs.

### Common Skin Diseases

**Treatment**—A very instructive report on the treatment of common skin diseases is given by F. R. Schmidt.<sup>20</sup> He states that the normal reaction of the unbroken skin is acid, varying between a pH of 4 and 6. When inflammation occurs and the continuity of the cutaneous surface is broken, a definite alkaline reaction sets in. Erythema is followed by vesiculation. The vesicles break and exudation takes place, with subsequent formation of crusts. This is the picture of the most common disorders of the skin, *dermatitis* and *eczema*.

The efficacy of applications of solutions of boric acid and aluminum acetate is thus explained on a sound basis. The alkaline reaction of the oozing surfaces

is neutralized by acid solutions, thus aiding epithelization to proceed normally. Weeping stops and new skin forms.

Affected areas should be wrapped in cheesecloth or gauze and kept wet with one of the following preparations:

**Saturated solutions of boric acid** are usually employed *hot*. The heat may be retained by covering the gauze with oiled silk or waxed paper. **Solution of aluminum acetate, N. F.**, on the other hand, is best used *cold*. One tablespoonful of this in a pint (500 cc.) of cold water usually is well tolerated. Compresses of this nature must be kept wet, otherwise they are detrimental.

The compresses should be removed at night. A mild astringent lotion is then applied. An efficient preparation of this kind is **calamine lotion, N. F.** The full strength lotion often causes "caking"; serum cannot escape, so that secretions are as effectively dammed up as if an ointment were applied. It is advisable, therefore, to dilute the lotion with an equal part of distilled water.

The use of diluted calamine lotion brings up the question of topical medication in dermatotherapy. Excessively strong remedies are constantly being prescribed. Best results are obtained with **mild soothing applications**. It is always best to begin the management of a dermatosis with a weak dilution of concentration of a favorite prescription.

**Dietary restrictions** are advisable in extensive cases of *dermatitis*. The intake of fluids and salt should be limited. Large doses of **sodium bromide in cinnamon water**, given at the onset of an attack, are helpful. Intravenous injections of **sodium thiosulfate** or **calcium thiosulfate** are often beneficial. The solution of sodium thiosulfate should be freshly prepared.

**Roentgen therapy** is often of great value in *subacute* and *chronic eczema*.

Hypertrophic, thickened patches grow soft after a few treatments. Acute eczema and dermatitis should not be exposed to Roentgen rays.

**Occupational Dermatitis**—Dermatitis due to contact with substances to which a worker is exposed in his occupation is now compensable in many states. The detection of the irritant is often difficult because of the complex chemical compounds used in industry. Installation of clean methods of manufacture has reduced the number of such cases.

**Prevention** of occupational dermatoses is possible. Persons in contact with irritating dust should not use greasy creams. **Greaseless creams** may be used as a protection against petrolatum and lubricating oils, and a **lotion** containing equal parts of **boric acid and alcohol** applied before and after work. Workers exposed to irritants should be taught how to cleanse their hands.

The use of patch tests prior to employment, in an effort to eliminate those applicants susceptible to dermatitis, is not feasible. Young untrained workers are most susceptible.

**Eczema in Infants and Young Children**—The co-operation of the mother is of paramount importance in treating infants and young children afflicted with this disease. Eczema in these little patients constitutes one of the most difficult chapters in cutaneous therapy. Failures and disappointments are frequent.

The commonest type of infantile eczema is presented by the baby with red, swollen cheeks covered with crusts. There may be patches of dermatitis on other parts of the body. Vesiculation and exudation are present. This form usually begins in the first few months of life.

The other type of eczema seen most frequently begins a little later in the first year. This may be preceded by exuda-

tion. The secretions disappear and the child acquires patches of dry, scaling skin interspersed with papules. The skin elsewhere is also often dry. These children are candidates for atopic dermatitis and have trouble with their skin throughout life.

The mother is often driven to desperation by the unsightly appearance of her child. He scratches himself constantly. A few words of assurance to the mother will help to allay her fears of damage to the child's health from lack of sleep. Eczema does not leave scars and the mother should be told this. (Letting grandmother have the child for a few weeks sometimes does wonders.)

It should be ascertained what factor or factors in the environment were new at the time of onset of the skin trouble. Had cod-liver oil or orange juice been added to the diet at that time? Was baby playing with a freshly lacquered toy? Had a dog joined the family? The possibility of contact with an irritant should be kept in mind.

The elimination of an allergen such as orange juice or wheat occasionally results in improvement. If scratch tests, however, show sensitivity to egg white, omitting eggs from the diet does not influence the eczema. The child may grow violently ill after eating eggs, but the eczema does not grow worse. Sensitization to egg is merely an indication of allergy, and is not the cause of the eczema. Hypersensitivity to egg and eczema are probably separate manifestations of a congenital idiosyncrasy.

Washing with certain soaps is allowed. A weeping skin is slightly alkaline in reaction and it has been learned recently that such a skin possesses a lessened resistance to alkalis. *Acidulated soaps of sulfonated oils* are now obtainable and are well tolerated by most individuals with sensitive skins. In lieu of such

soaps, the following procedure is often of value: The child is first scrubbed with ordinary soap, leaving the lather on the skin for several minutes. This is removed with cold water. After drying, a 5 per cent *aqueous solution of tannic acid* is daubed on lightly. *Borated talc* is then dusted on the lesions to prevent the linen from staining. This sequence is repeated several times daily. The exudation tends to stop, and the child is comfortable for several hours after each treatment.

Eczematous patches may be covered with *zinc paste* containing 15 to 25 per cent of pure (not synthetic) *naphthalan*. *Crude coal-tar* may be used instead, beginning with a concentration of 3 per cent and increasing this as improvement sets in.

A child that is covered from head to foot with weeping, crusting dermatitis does well in the *bath tub*. Itching stops and crusts are washed away. Epithelization is hastened by adding a little *boric acid to the water*.

**Atopic Dermatitis** The child whose dermatitis begins with dry, scaling areas of inflammation often has parents who have hay-fever, asthma or urticaria. He may develop hay-fever or asthma later in life. Throughout the years of adolescence he may have several attacks of itching dermatitis that leave their imprint on the skin. These brownish, lichenified areas of neurodermatitis are characteristically located in the bend of the elbows, sides of the neck and around the eyes.

Persons suffering from this disease are greatly to be pitied, because as yet no remedy has been found to cure it. A *change of climate* often benefits these patients, solely because they are removed from a harmful environment. A nagging, neurotic mother may be a precipi-

tating factor in bringing on an attack of itching, or it may be house dust.

During an exacerbation of the disease, most patients obtain a maximum degree of relief from the application of *cold, wet dressings of aluminum acetate*. When the attack has subsided, a *weak ointment of crude coal-tar* may be used on the patches of thickened skin.

The patient should be helped in securing as much *mental and physical relaxation* as is possible under the circumstances of his life. *Short rest periods during the day* are indicated. The quieting effect of *warm baths* is beneficial, provided that the skin is not too dry. The precocious, nervous child should be restricted in his mental and physical activities. An attempt must be made to ease the financial, marital or familial burden under which the patient is suffering.

In those individuals exhibiting a positive reaction to the intradermal injection of minute amounts of *house dust* or *fungi* of the *Trichophyton* and *Alternaria*—*Hormodendrum* — *Penicillium* group, considerable benefit may be anticipated from the use of *vaccines* made from these substances. This is especially true of those patients showing a strong reaction to the dust collected in a vacuum cleaner in their own homes. Desensitization to animal dander and pollens has not proved successful.

In a small group of such cases the administration of small doses of *thyroid extract* produces striking improvement. The skin appears to soften and the itching diminishes.

**Acne**—Acne is a disease whose social and economic aspects are of vast importance. An unsightly complexion bars many persons from employment of various kinds. The social adjustment of an

individual to his environment is made difficult by blemishes on his face.

Since the cause of acne is still in doubt, it follows that any disturbance of the internal organs should be overcome on the theory that thus a possible etiologic factor is being eliminated. *Gross errors of diet and hygiene*, as well as *irregularities of elimination and menstruation*, should be corrected.

Many young patients are drinking too much milk. A few months ago a boy of 17 with a severe acne gave a history of drinking 3 quarts of milk daily, in addition to a full diet of other foodstuffs. His mother wondered whether he was eating enough. A reduction to a pint of milk a day, with prohibition of chocolate, nuts and peanut butter greatly improved the condition of the acne.

The anemia of young women may be banished with adequate doses of tablets of *ferrous sulfate*. Vitamin therapy, although carried to the limit of the patient's pocketbook, has not proved of lasting benefit in the experience of the writer.

Patients should indulge in a reasonable amount of *outdoor exercise*. *Showers in the morning* before going to work are recommended, in conjunction with *abdominal massage* which the patient can carry out himself. *Correct posture* is equally essential.

Persons with seborrhea and acne should *wash the face* 2 or 3 times daily with a *neutral soap* which they have learned does not irritate their skin. Vigorous rubbing with a washcloth or complexion brush must be avoided. The *lather* is allowed to remain on the face for a few minutes before it is washed off with cold water.

The *nightly application of a solution of borax to the face* is advisable. The keratolytic action of borax serves to remove the scale that plugs the openings

of the sebaceous glands. It allows the skin to breathe again, so to say. The patient is told to begin using  $\frac{1}{2}$  teaspoonful of borax in a pint (500 cc) of hot water. This is applied and the face dried.

A small amount of a **sulfur lotion** is then patted on the face and allowed to remain over night. The use of colloidal aluminum silicate (bentonite) provides a better vehicle for suspension of sulfur than does lime water.

℞ *Precipitated sulfur* 3i $\frac{1}{4}$  (7.0 Gm.)  
*Camphor* gr viifs (0.5 Gm.)  
*Bentonite solution*  
 (2 $\frac{1}{2}$  per cent) f3iv (120.0 cc.)

Sig—Apply to face at night

This lotion should be discontinued at the first sign of irritation. The use of a small amount of the lotion at the start of treatment and gradually increasing it at each application will usually prevent this trouble.

In mild cases of *shiny noses accompanied by only a few papulopustules* it is often sufficient to prescribe a *talc* containing 2 per cent **colloidal sulfur**. This is dusted on the face twice daily.

**Blackheads** may be removed by applying a liberal coat of **cold cream containing 3 per cent resorcinol**. After an hour or so a towel wrung out of steaming water is laid on the face. Or the patient may place his head over a wide-mouthed kettle of steaming water to which  $\frac{1}{2}$  teaspoonful of **spirit of camphor** has been added. Expression of the blackheads with a small implement of the kind obtainable at any drug store is then relatively simple.

The care of the scalp is essential to the successful management of acne. This applies equally well to seborrheic dermatitis of the face. Most of these patients are beset with *dandruff*, usually accompanied by itching.

**Frequent shampoos** with ordinary soap or **tincture of green soap** are indicated. A few drops of the following lotion, well rubbed into the scalp several times a week, suffice to allay the itching and scaling.

℞ *Resorcinol monohydrate* 3i $\frac{1}{4}$  (5.0 Gm.)  
*Talc* 3i $\frac{1}{4}$  (5.0 Gm.)  
*Salicylic acid* gr ssiii (1.5 Gm.)  
*Castor oil* 3i $\frac{1}{4}$  (3.0 cc.)  
*Alcohol* (70 per cent) q s f3iv (120.0 cc.)

Sig—Apply to scalp

**Rosacea** Rosacea may be associated with acne, but its mechanism of production is entirely different. The disease occurs chiefly in women over 30 years of age. A characteristic feature of these cases is weakness of the abdominal musculature and ptosis of the internal organs. A fluoroscopic examination reveals a delayed emptying time of the stomach. A low gastric acidity is often found. The muscular hypotonia is extended to include the smooth muscle fibers of the blood-vessels of the face. Poor muscular tone of this character cannot withstand the strain of constant dilatation and finally gives up the fight altogether. The vessels remain dilated and the clinical picture of flushing, dilated blood-vessels and purplish discoloration is complete.

Measures should be adopted to prevent this cycle of events. **Hydrotherapy, correct posture and massage** are important adjuncts of therapy. **Avoidance of alcohol and hot and spicy foods** is manifestly necessary. To aid digestion the following prescription has proved of value:

℞ *Hydrochloric acid* . . . . . f3iifs (10.0 cc.)  
*Pepsin scales* . . . . . 3iifs (10.0 Gm.)  
*Elix lacto peps.* . . . . . f3iv (120.0 cc.)

M. Sig.: Take 1 dram (4 cc.) in a little water after meals, through a glass tube.

The irritating action of soap should be avoided. An **ointment** containing

from 2 to 4 per cent of *ichthyl* and 4 per cent of *sulfur* incorporated in a greaseless base has proved beneficial. This is applied at night.

**Psoriasis**—A *change of climate* often produces a decided improvement in psoriasis, especially in those cases complicated by arthritis.

No specific remedy against this disease exists. Nevertheless, the patient must be warned against the danger of neglecting treatment. Untreated psoriasis has a tendency to spread over the entire body. Patients with psoriasis should get as much *sunshine* as possible, *wear light, white clothes*, and apply an ointment to the lesions at least every other night. Those who are eating too much fat should reduce its intake. A little desiccated *thyroid extract* taken daily occasionally works wonders. In other patients a course of *Asiatic pills* brings an involution of the lesions.

**Whole blood injections** have proved of value in preventing a fresh spread of the disease, especially if the attack occurs in the summer or winter.

The choice of a topical medicament is difficult. Depending on the amount of cutaneous involvement, varying strengths of *ammoniated mercury ointment* may be used. For large areas it is best to begin with a 3 per cent ointment containing 2 per cent *salicylic acid* with which to remove the scales. A patient who has never rubbed mercury on his skin should first be tested for possible idiosyncrasy to this drug. Some patients do better with an *ointment of crude coal-tar*, especially if they own a *sun lamp* which they can use in conjunction with the ointment.

**Herpes Simplex and Zoster**—The author practiced *vaccination* of patients afflicted with simple herpes for many years. A vesicle is opened and its contents scarified into a previously selected

area of skin. Local reactions occur in about 30 per cent of patients treated in this manner, and these individuals remain free from further attacks. Lately, the use of *smallpox vaccine* has produced better results.

The *pain* of herpes zoster often responds favorably to iodine medication. Intravenous injections of *sodium iodide* in conjunction with large doses of *potassium iodide* by mouth seem to ameliorate the suffering. *Heat* applied *locally*, followed by dusting with a *borated talcum powder*, is beneficial.

### Varicose Ulcers of the Leg

**Treatment**—Varicose ulcers have long been considered one of the most troublesome conditions confronting the general practitioner and to some extent even the specialist. The mass of literature on the subject, giving a variety of modes of treatment and technic as numerous as the publications themselves, shows the difficulties which the physician has to face.

In order to clear up a varicose ulcer, according to Isaak,<sup>21</sup> it is necessary (1) to eliminate the cause, (2) to stimulate the granulation of the ulcer, and (3) to improve the circulation of the blood and the lymph.

If the ulcer is not caused by thrombophlebitis, the *varicose veins* first must be obliterated by the *injection method*. In case of thrombophlebitis, however, the injection method should under no circumstances be employed as long as active inflammatory processes are present; and even after the thrombophlebitis has subsided, caution must be exercised, since the condition is apt to flare up again easily. Those varicose veins which surround the ulcer or are in its proximity should be sclerosed first in order to restore better blood circulation to the ulcer. The artificial inflammation of the

vein and occasionally of the surrounding tissue, caused by the obliteration of the vein, results in an increase of leukocytes in that tissue to the extent that they form a wall or a barrier around the ulcer.

Regarding the *stimulation of granulation tissue*, the following technic has been used in the New York Post-Graduate Medical School of the Columbia University Clinic for the past 2 years after having been successfully tried in private practice for a number of years. After protecting the surrounding skin by a thick layer of **zinc oxide paste**, the ulcer itself is covered with a few layers of thin genuine **silver leaf**, which is generally used by sign painters to paint silver letters on windows and which is available in 3 brands, an American, a German, and a Japanese, the American being found to be the thickest and therefore the best. They can be purchased in any paint store.

The ulcer is then **covered with a thick layer of cotton and bandaged tightly**. The silver leaf treatment has a double effect, the air-tight occlusion of the ulcer forming a wet chamber, a treatment formerly accomplished by adhesive strappings or a cover of lead or zinc foil, and having also an apparent catalyzing effect. Fresh red and healthy granulations under the silver leaf appear quickly without having a tendency to decay. The oozing of the wound decreases remarkably, and the fetid odor of the ulcer rapidly disappears. Among the ulcers treated at the clinic was a Roentgen ray ulcer occurring on the hand. It did not clear up when treated with aloe vera leaf, but responded quickly to the treatment with silver leaf. It is important to protect the surrounding tissue with zinc oxide paste, in order to prevent maceration of the skin by the secretion of the ulcer. The cotton which has

been placed on the silver leaf is used to absorb the secretion. It is understood that the ulcer must be dressed again in 3 to 8 days, according to individual needs. If there should be much secretion, a burning pain will appear and a new dressing of the ulcer is indicated. The surrounding tissue is then **washed with purified petroleum benzine, ether or olive oil**.

To *restore blood circulation* in the leg to a healthy state, **zinc-gelatin bandages (Unna's boot)** may be applied from the toes up to the knee. Formerly the application of these bandages was rather troublesome and wearisome, but there are now available several types of such ready-made bandages manufactured in this country, which greatly facilitate the dressing, as they are ready to use after removal from their containers. The bandage must be applied tightly in the following manner:

Elevate the leg for a few minutes. After local treatment of eczema or ulcer and application of padding, start bandaging on the lateral side of the foot just above the toes, and then proceed under the sole and around the inner side of the foot, so that the arch is lifted properly; repeat this turn once or twice, and then bring the bandage up above the angle in a figure-of-eight and repeat a few times as needed, until the whole foot and the lower part of the leg are covered with the bandage. It is advisable to cut off the bandage now and again in order to get a more even dressing, according to the configuration of the leg, without pulling the bandage unevenly. Apply the bandage so that 1 layer covers one-half of the former layer and they both form a solid and uniform mass. Such a dressing can, if necessary, be worn for 2 or 3 months before removal. It is possible to treat the ulcer locally without removing the supporting dressing by cutting a window in the bandage. A **water-tight rubber bath boot**, now on the market, enables the patient to bathe and provides a water-proof protection for the zinc-gelatin bandage.

Only when the surrounding tissue of an ulcer is covered by **eczematous lesions** which ooze severely is local treatment, consisting of dress-



*ings wet with boric acid* or painting with *methyl-rosaline (gentian violet)*, 2 per cent aqueous solution, needed.

It is understood that the varicose ulcer, owing to its varying causation, shows remarkable differences in its process of healing, depending on whether the ulcer was caused by chronic congestion or by thrombophlebitis, or whether it is situated in pathologic tissue or in relatively normal skin. Often the small but deep crater-like ulcers, usually found in highly inflamed, reddened and swollen skin, which are caused by thrombophlebitis, have shown a tendency to heal slowly. It even was found in some cases that such ulcers would not respond to several weeks of treatment and that sometimes during that period they even would enlarge somewhat in spite of injections into the varicose veins, until finally they suddenly started to heal. This was, no doubt, due to the fact that the inflammation at the root of the ulcer had been arrested. Flat ulcers surrounded by heavily damaged eczematous and erythematous, or also by atrophic or callously hypertrophic, tissue showing little edema and often covered by thick, hard crusts, heal very slowly, while large deep ulcers caused by embolic occlusion of a vein and usually surrounded by relatively healthy tissue granulate quickly along the edges. These ulcers can be observed to close gradually under treatment, with granulation proceeding from day to day and covering a large area within a short time. It is amazing to see how an ulcer almost the size of the palm, which previously failed to respond to every other therapy, will heal completely within a few weeks after sclerosis of the veins, treatment with silver leaf and bandaging, while the patient is up and about.

*Thrombophlebitis* of the leg can be treated successfully by local application of 10 per cent *ichthammol-zinc paste* and *zinc-gelatin bandages* without confining the patient to bed. In cases of this condition particularly, such a dressing should be worn for a long time.

If *varicose veins* are hidden in *edematous tissue* a *zinc-gelatin bandage* is employed to reduce the swelling, and when the varicose veins are visible again, they can be treated in the usual manner.

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## GYNECOLOGY AND OBSTETRICS

By ARTHUR FIRST, M.D

## I. GYNECOLOGY

## AMENORRHEA

**Treatment**—Cases of delayed menstruation, now generally ascribed to temporary endocrine dysfunctions, might in fact occur despite normal hormone secretion and be due to abnormally decreased vascular responsiveness. It therefore seemed worth while to Soskin, Wachtel and Hechter<sup>1</sup> to attempt to treat such cases by pharmacologic rather than by endocrine means.

It was decided to potentiate the naturally occurring acetylcholine in the uterine endometrium with *prostigmin methylsulfate*, a synthetic physostigmine-like substance which is commercially available. In animals and women prostigmin did not terminate a pregnancy in a single instance, even when relatively huge amounts of the drug were given.

In cases of delayed menstruation in which early pregnancy was ruled out by the history and physical examination, supplemented by the Friedman test when necessary, prostigmine invariably precipitated the menstrual flow. The flow started as soon as half an hour after the injection in 1 instance. The longest interval between the last injection and the beginning of the flow was 78 hours. The average time which elapsed was 28 hours. In some instances the amount of flow was somewhat heavier than that usually experienced by the patient, though not alarmingly so. With 1 exception, all the patients reported normal menstruation at their next regular period.

In most instances the patients were injected intramuscularly, with 2 cc. of

1 2000 solution of prostigmin methylsulfate on 3 successive mornings

The constancy of the results in menstrual delay and the lack of effect on pregnancy make it possible, the authors claim, to use prostigmin as a combined treatment for menstrual delay and a therapeutic test for pregnancy

## CERVIX

## Carcinoma

From 1913 to 1939 inclusive, 910 patients with carcinoma of the cervix were admitted to the Gynecologic Service of the University Hospital. In this case series, the cancer was recognized some time after supravaginal hysterectomy had been performed in 43 patients, an incidence of 4.7 per cent. In the second series, which comprised the 1117 patients who had been admitted to Philadelphia General Hospital since the establishment of its Radiologic Department, in 1922, supravaginal hysterectomy had been carried out prior to the diagnosis of cancer in 24 cases, an incidence of 2.15 per cent.

Behney<sup>2</sup> analyzing these cases notes that carcinoma of the cervix after supravaginal hysterectomy behaves similarly to the same disease when the fundus is retained. Its response to treatment is no worse than that of "cervix" cancer in general, and in some clinics is better.

Approximately 40 per cent of "stump" cancers recognized 3 years after subtotal hysterectomy, or within 6 months of the appearance of the first symptoms, were living and well 5 years after treatment.

Subtotal hysterectomy appears to improve the chance of cure if performed before carcinoma of the cervix has been acquired.

The probable development of vesicovaginal fistulas is greater than when the fundus is present. Fistulas are more often due to the disease than the result of treatment.

Meticulous examination of the cervix should be made a part of every gynecologic examination. Areas which are normal should be removed for histologic study. These principles are no less important when removal of the fundus is contemplated.

Complete hysterectomy is an excellent manner of dealing with disease of the cervix when the fundus is to be removed. However, in the hands of those whose experience is limited, supravaginal hysterectomy, combined with trachelectomy, is satisfactory and less hazardous.

An experiment in cancer control by making periodic pelvic examinations of 1000 well women 30 years of age and over twice a year for 5 years is reported by Macfarlane, Fetterman and Sturgis.<sup>3</sup>

These examinations consisted of:

1. A careful bimanual pelvic examination.
2. A careful inspection of the cervix in a good light.
3. The application of Lugol's solution to the cervix according to the technic of Schiller.
4. The use of a blunt tipped pocked probe to detect friability of tissue according to the technic of Chrobak.

At first quite a few biopsies were performed. As the experiment proceeded, the investigators were more inclined to recommend the removal of cervical pathology *in toto* by means of surgery or conization.

In the first 1000 examinations 4 malignancies of the uterus were found.

In addition to these early malignancies, 357 benign lesions were found in 318 volunteers. These comprised papillomas 1, leukoplakic areas 6, polyps 43, endocervicitis and cervicitis 48, inflammatory erosions 189 (simple 50, papillary 53, follicular 1, not specified 85), myomatous tumors 66, ovarian cysts 4.

Upon the second examination of these 1000 volunteers, after an interval of 6 months, no malignancies were found. Old lesions were present in 177 women, 76 new lesions were found in 69 women. These new lesions comprised leukoplakic areas 4, polyps 15, endocervicitis and cervicitis 19, inflammatory erosions 24, (simple 10, papillary 10, follicular 2, not specified 2), myomatous tumors 14, ovarian cysts 0.

**Relief of Pain in Carcinoma of Cervix**—Todd<sup>4</sup> has pointed out that 2 types of pain, visceral and somatic, were experienced in advanced carcinoma of the cervix uteri and that they could be differentiated clinically. The author investigated 33 cases: 15 of visceral pain and 18 of somatic. The treatment advocated was *presacral neurectomy* for visceral pain and intrathecal injections of *absolute alcohol* for somatic. When the appropriate method was used, the percentage of success was high.

In the past 2 years Todd has continued this research in a further series of 55 cases and reports relief in 90 per cent. In investigating the cases a careful history and description of the pain is taken, a neurologic examination is made, examination under anesthesia, cystoscopy, sigmoidoscopy and exclusion of pyometra are done and roentgenography of the lumbosacral spine and pelvis and pyelography complete the investigation.

Then an assessment is made of the type of pain and of the nerve path concerned.

Todd regards pain of sufficient severity to prevent sleep unless sedatives are administered as the most reliable indication of intractability. A week or even longer may be necessary for deciding whether the pain is minimal and the patient over-reacting to it. He is convinced that it is most important to have a precise objective phenomenon, such as interference with sleep, when attempting to assess and treat patients alleged to have severe pain.

As regards visceral pain, the commonest cause is ulceration of the rectum, malignant involvement of the base of the bladder, or pyometra. Either direct local therapy or presacral neurectomy has almost always given relief. In cases associated with an advancing malignant process an alternative therapy to presacral neurectomy consists in injections of alcohol so administered as to affect the upper lumbar roots, and the author thinks this will replace neurectomy in the malignant cases.

Intrathecal injections of alcohol have been given in 28 further cases of somatic limb pain. The average duration of relief was 3 months. Two patients are still alive, having been treated over 2 years ago, and the relief has persisted, though in one the pain is beginning to recur. Failure to achieve relief probably indicates a technical imperfection or the presence of cord compression or is due to drug addiction. It is emphasized that injections of alcohol should be given only in the presence of malignant disease.

The use of *cobra venom* for intractable pain associated with incurable pelvic cancer is advocated by Kelso.<sup>5</sup>

The cobra venom is supplied in 1 cc. ampoules, each representing 5 mouse units. It was given intramuscularly. The

initial dose was 0.5 cc., with succeeding daily doses of 1 cc. until relief was obtained, or until 10 ampoules were given. It was noted that in 12 of the cases reported the estimated relief of pain ranged from 85 to 100 per cent. While there were no serious untoward sequelae, there were definite local and systemic reactions encountered, manifested by transitory shock and cerebrovascular disturbances. The use of cobra venom, the author feels, should be limited to carefully chosen cases and its effects closely observed until its physiologic action is better known to the clinician and its ultimate results more clearly defined.

### Endocervicitis

The treatment of endocervicitis with *CO<sub>2</sub> snow (dry ice)* is reported by Weitzner.<sup>6</sup> This investigator applied topically a rod of solid carbon dioxide to the cervical canal for from 60 to 90 seconds in the treatment of 325 cases of endocervicitis. The first patient was treated in May, 1934, and the last in December, 1935; 70 per cent of the patients required only 1 treatment for a cure (cases with erosion responded more readily to the treatment), 15 per cent required 2 treatments and 15 per cent were treated 3 or more times. No postoperative sequelae, such as bleeding, inflammation or stenosis of the cervical canal, have been observed after 2½ years of follow-up. Inspection of the treated areas 24 hours after treatment shows them to be covered by a grayish pseudomembrane. Seven days after treatment the areas are no longer so covered. The cervix bleeds readily to touch. Biopsies taken at this stage show areas of necrosis still present, but in general the picture is one of early regeneration, especially in the region of the stratified squamous epithelium. Inflammatory changes are absent. From 10

to 17 days after treatment macroscopic signs of healing are visible. From 3 to 4 weeks after treatment the entire area of the erosion is covered by stratified epithelium. Eight weeks after treatment cervical biopsy shows complete cure.

In 31 of 111 cases atypical cells were found on microscopic study in atypical arrangement, apparently invading the surrounding tissue. These cells resembled the earliest stages of the cervical malignant changes to such an extent that treatment was suspended pending further study and follow-up.

On the basis of 201 biopsies taken from the cervixes showing the atypical cells the following statements are made: (1) There were erosions in all cases prior to treatment. (2) The number of treatments had no influence on the development of atypical cells. (3) The atypism was observed as early as 1 week after treatment. (4) The duration of the atypism ranged from 3 months to more than 2½ years. (5) Cases with atypical cells showed macroscopically a perfectly smooth normal cervical surface. Thus it appears that these nests of atypical cells may be regarded as signs of increased activity of the stratified squamous cell epithelium in a healing erosion and not true malignant changes.

## CHEMOTHERAPY

The value of chemotherapy in obstetrics and gynecology is discussed by Douglas.<sup>7</sup>

**Sulfanilamide** was the drug used in all patients in this study, excepting those with pneumonia, where **sulfapyridine** was employed. The present study is based on an analysis of 180 patients treated during the past 3 years in the New York Lying-in Hospital. There were 115 patients with urinary tract

infections, 86 of whom were obstetric, and 29 gynecologic; 34 patients had gonorrhea, 20 puerperal or postabortal infections, 7 pneumonia, and 4 miscellaneous infections. Included in this latter group, there are 1 case of lymphogranuloma venereum and 1 patient with subacute bacterial endocarditis.

All patients were treated in the Hospital as bed patients, with the exception of a few with chronic urinary tract infection who were treated by means of 1 or more courses of small dosage, consisting of 22½ grains (1.5 Gm.) per day for 5 days while attending the Out-Patient Department. Unless some reason to the contrary existed, all medication in the hospital was given at 4-hour intervals, both by day and by night, combined with an equal amount of **sodium bicarbonate**. Blood hemoglobin estimations and the white blood count were done on all hospital patients at least every second day. The drug concentration in the blood, and the urine if indicated, was done at similar intervals. An attempt was made to control the fluid intake, unless contraindicated by fever, so that the urinary output would approximate 1000 cc per day. No dietary restrictions were employed. **Nicotinic acid** was used with some apparent success in a number of the recent cases in an attempt to eliminate some of the minor toxic symptoms.

### I. Urinary Tract Infections

In general where "small" dosage, "30 grains (2 Gm.) daily," was employed the blood level of free sulfanilamide was usually 2 to 4 mg. per cent and the urine concentration about 40 to 75 mg. per cent. Where the "medium" dosage, 60 grains (4 Gm.) daily, was used the figures were 5 to 7 mg. per cent in the blood and 100 to 150 mg. per cent in the urine. The concentrations in the

blood with "large" dosage, 105 grains (7 Gm.), varied from 7 to 15 mg. per cent and in the urine from 200 to 400 mg. per cent.

In the evaluation of results in obstetrics and gynecologic urinary tract infections, the following fundamental considerations must be kept constantly in mind.

Organisms of the colon aerogenes group are the chief cause of urinary tract infections, complicating obstetric and gynecologic conditions. The urine under such circumstances can usually be rendered sterile with varying amounts of sulfanilamide. Subsequent follow-up is necessary because reinfection may recur if the same conditions subsequently exist as were present prior to the initial infection.

The urinary tract should be free from organisms before the patient is finally discharged. It is usually more difficult to render the urine sterile where the infection has been severe or has existed over a long period of time.

In antepartum bacilluria and definite pyelitis, the urine was rendered bacilli-free and kept so in 10 of 13 cases. This fact is of great importance in the prevention of pyelitis. The earlier the diagnosis and treatment, the better the results will be.

The primary infecting organism was eliminated from the urinary tract in 69 per cent of a group of 115 obstetric and gynecologic patients with bacilluria or pyelitis, who were treated with sulfanilamide.

## II. Gonorrhea

1. The author points out that the original diagnostic procedure and all follow-up examinations should include cultures as well as smears.

2. Adequate dosage (75 to 90 grains—5 to 6 Gm. daily) for about 7 days is

necessary for the successful treatment of the disease.

3. Cure is effected during the first 48 hours of therapy in the majority of patients, but occasionally it takes at least 5 days.

4. Gradually decreasing dosage of the drug is not indicated following the initial "high" dosage.

5. Hospitalization is essential for the satisfactory and safe employment of sulfanilamide.

6. Haphazard treatment with inadequate dosage often renders the patient asymptomatic. Such individuals may be a serious menace to society by spreading the disease, in addition to bringing discredit to this form of therapy.

## III. Puerperal and Postabortal Infections

Douglas points out that prophylactic cultures should be taken where later infection appears probable, that sulfanilamide is usually indicated in infections caused by hemolytic streptococci or *B. zeichii* and that the drug is not known to exert any definite therapeutic effect in other types of infection.

## CONTRACEPTION

A selected group of 197 contraceptive patients from a hospital obstetric service has been studied by Beebe and Gamble<sup>8</sup> for variations in the risk of conception associated with contraceptive practice. It has been shown that before admission:

1. There were the expected religious and occupational differences in the extent of contraceptive practice.

2. While contraception was practiced the risk of conception was almost 60 per cent below that incurred without contraception.

3. Withdrawal, douche or condom, used alone or in combination, was relied

on in 90 per cent of the contraceptive practice.

4. The risk of conception while the condom was used alone was 80 per cent below the noncontraceptive level, the corresponding figure for the douche being 40 per cent.

After the hospital had given advice to this interested group:

1. The relative dependence on contraception increased from 65 to 95 per cent.

2. The pregnancy rate for contraceptive practice declined about 70 per cent below the preclinic level, all methods contributing to the increase in protection; the contraceptive rate was about 85 per cent lower than the preclinic non-contraceptive rate of this group.

3. Only 65 per cent of those who purchased the supplies ever used them, and of these 25 per cent were continuing their use 20 months later.

4. It seemed that the technic of instruction, in suggesting alternatives, and the relative inaccessibility of supplies for some had combined to discourage the use of the method advised.

A study of 500 contraceptive cases from private practice is presented by Warner.<sup>9</sup> In 94.3 per cent of these patients contraception was admittedly being practiced before the medical consultation. The cases are drawn from various religious, age and economic groups. The women requested contraceptive advice for a variety of health, psychologic and economic reasons. More than 50 per cent (276) of the women in this study were employed of necessity. Ninety per cent of the "premarital" group stated that they had to continue working after marriage. Half of the group of 500 stated that inadequate income was their main reason for wanting to avoid further pregnancies.

The majority of women sought contraceptive advice during the first year of marriage, the remainder from 1 to 30 years after marriage. The trend among the younger group is toward obtaining contraceptive advice premaritally.

Fifty-seven per cent of the unmarried and 6.5 per cent of the married women had intact hymens. Most of these required medical dilation. Thirty-eight per cent of those seeking premarital advice were already having sex relations.

Fifty-three per cent of the women had planned pregnancies, usually 1 or 2 children, the average being 1.8 children per mother. Of all the pregnancies, 60 per cent were accidental and resulted from the failure of various types of contraception. An analysis of these failures is given. Five per cent of the total group had been pregnant before marriage. Very few accidental pregnancies occurred in the group instructed premaritally.

A most important observation was that medically prescribed contraceptive advice reduced the number of abortions by four-fifths. Forty-two per cent of the 252 parous women had had abortions. Sixty-four per cent admitted to 1 abortion and 36 per cent had had 2 or more abortions. The majority of abortions occurred in married women.

The most frequent method which the author prescribed was the vaginal diaphragm lubricated with a contraceptive jelly or cream (90.8 per cent of the cases). The sizes most frequently prescribed were, in order, 80 mm., 75 mm., and 85 mm. This method proved to be 97.6 per cent effective and improved marital adjustment. The most frequent causes for sexual dissatisfaction are analyzed.

Every "premarital" couple expressed the desire for offspring in the future. They felt the need for temporary contraceptive advice and wanted the as-

surance that the method would not cause sterility.

### DYSMENORRHEA

**Treatment**—The hypodermic use of *adrenalin chloride* for relief of menstrual cramps is reported by Wolfe.<sup>10</sup> He gave 7 patients with dysmenorrhea hypodermic injections of epinephrine on the theory that contraction rings and menstrual cramps are produced by spasm of the cervical and uterine muscle fibers and that they can be relieved through the autonomic nervous system by stimulating the sympathetics. Five of the patients had a less severe type of disorder; they responded promptly and experienced relief within 5 minutes of the injection.

Abarbanel<sup>11</sup> investigated the percutaneous administration of *testosterone propionate* for dysmenorrhea in 10 patients. The method is indicated when patients object to injections, when they cannot come regularly to the dispensary, in those previously treated by injection with few residual symptoms and in those who, having to leave town, cannot secure the injections. Each patient is urged to receive parenteral therapy first, as the required dosage by this route affords a guide to the amount necessary percutaneously. Patients who do not respond to parenteral therapy usually will not respond to cutaneous administration.

The dosage required by the percutaneous route is from 3 to 6 times as great as that which is necessary for the subcutaneous route, depending mainly on the vehicle. Sesame oil has proved more effective than any of the ointment bases tried. The areas utilized for percutaneous administration have been the axillary region, the inner part of the thighs or the deltoid region. If the gynecologic examination is negative, the patient is told to begin percutaneous ad-

ministration from 10 days to 2 weeks before the expected onset of the next menstruation. If the uterus is small or anatomically misplaced, or both, or if the patient is 30 or more years old, she is advised to begin applications from 4 to 5 days after the period is over and to continue them for the remainder of the cycle. The total dosage per cycle has ranged from  $1\frac{1}{3}$  to  $1\frac{1}{2}$  grains (20 to 90 mg.) of the testosterone. Each patient must be treated individually and no set dosage schedule can be outlined.

After 3 successive periods with little or no discomfort, therapy is discontinued for a month to observe whether improvement is maintained. If not, treatment is repeated. Only 1 of the author's 10 patients was not relieved.

**Palliative Treatment**—In this study a combination of 5 grains (0.3 Gm.) of *acetylsalicylic acid*, 3 grains (0.2 Gm.) of *phenacetin*, and  $\frac{3}{4}$  grain (0.045 Gm.) of *propadrine hydrochloride* was used by Ainlay<sup>12</sup> for the palliative treatment of dysmenorrhea.

The propadrine hydrochloride is a marked antispasmodic and decongestant without side effects. It is far superior to ephedrine as an antispasmodic and much less toxic.

The patients were given 3 capsules daily (except in the most severe cases, when the patient received 1 every 3 hours) at the very first onset of distress, and continued until the third day of the period. Pain after the third day is not relieved well by this preparation and should lead one to suspect some organic lesion. This preparation, the author found, offers marked relief for the majority of women who suffer distress and depression during the menstrual period.

### Ovarian Dysmenorrhea

Ovarian dysmenorrhea, according to Browne,<sup>13</sup> is a definite clinical entity



with characteristic symptoms and signs which allow of an accurate diagnosis. It is present alone in about 11 per cent of all cases of dysmenorrhea but may be associated with dysmenorrhea of uterine origin, thus constituting "mixed" dysmenorrhea.

*True ovarian dysmenorrhea*, the author claims, can be completely cured by **bilateral ovarian denervation**. He did not observe any ill effects following this operation. In the *severe and intractable dysmenorrhea* of uterine and ovarian origin both **bilateral ovarian denervation** and **presacral sympathectomy** are probably indicated.

In an effort to separate clinically uterine from ovarian dysmenorrhea the author devised a test employing a sound. In several cases a small intrauterine bag inflated to 5 cc. capacity was used, with full aseptic precautions, to test for uterine pain. In others, when the fallopian tubes of the patient were blocked, Rubin's apparatus was used up to 300 mm. of mercury pressure. From these methods the author concluded that typical uterine pain is accurately referred to the midline of the lower part of the abdomen in the immediate suprapubic area, although it may sometimes reach as high as the umbilicus. This was true in 49 per cent of the patients examined. In 11 per cent of somewhat exceptional instances of uterine dysmenorrhea the passing of a uterine sound produced atypical referred pain in some other part of the lower abdominal area. In most of these there was some palpable pelvic abnormality. The passing of the sound was painless in approximately 36 per cent of the patients, many of whom were not suffering from dysmenorrhea; it produced pain referred exactly to the umbilicus in 2 per cent, and to the midline of the vulva about the position of the clitoris in the other 2 per cent.

Pathways for painful ovarian stimuli exist in the ovarian nerves. The neurogenic eitologic theory of ovarian dysmenorrhea is accepted by the authors as the most likely and his microscopic material confirms these observations. Sclerocystic ovarian changes are constant in severe ovarian dysmenorrhea and are probably secondary to pre-existing ovarian nerve lesions. Cervical dilation, with or without uterine curettage, relieves only those cases of uterine dysmenorrhea in which there is no serious premenstrual discomfort or pain. It is pointed out that Cotte's 60 per cent cure rate of uterine dysmenorrhea by **presacral sympathectomy**, when considered along with the author's 11 per cent rate in cases of isolated ovarian dysmenorrhea following **bilateral ovarian denervation**, suggests that the remaining 25 to 30 per cent of cases of severe dysmenorrhea are of the "mixed" type or, possibly, of endocrine origin.

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## HORMONES IN GYNECOLOGY

### Androgen Therapy

An evaluation of androgenic therapy in gynecologic practice is presented by Huffman.<sup>14</sup> Effects in 22 women who received androgenic therapy parallel those produced in laboratory animals by injections of **testosterone propionate**. In the author's cases, functional *uterine bleeding* was inhibited by the male sex hormone. In this group, no notable masculinizing changes developed, except occasional temporary hypertrophy of the clitoris. Three of these patients have been under observation for more than 2 years.

Testosterone propionate will bring about a cessation of genital activity in human beings as it has been observed to do in the adult female rabbits and rats.

This effect is the result of pituitary rather than ovarian inactivation. The changes produced by the male sex hormone are temporary, with resumption of cyclic phenomena in the genitalia after administration is discontinued. When large doses of testosterone propionate (over  $5\frac{1}{2}$  to  $7\frac{1}{2}$  grains—350 to 500 mg.) are injected over a considerable period of time, temporary masculinizing changes, especially hypertrophy of the clitoris, may appear. Inhibition of activity in the lactating breast after the administration of testosterone propionate has been observed clinically and has been demonstrated histologically in animals. Reports in the literature indicate that reproduction is possible and that normal young have been born to human beings who have received male sex hormone prior to their pregnancies.

There is considerable evidence to suggest that androgenic therapy has a place in the treatment of *functional uterine bleeding*, *mastalgias* and *puerperal breast engorgement*, and for the *inhibition of lactation*. Further investigation of its use in *dysmenorrhea* and the treatment of *menstrual molimina* seems indicated. The use of male sex hormone may, perhaps, be advantageously used in preference to the estrogens in certain selected instances of *menopausal disturbances*.

Further studies on the androgen therapy of gynecologic disorders is reported by Greenhill and Freed.<sup>15</sup> Twelve patients have been more recently receiving testosterone propionate. This group consists of 3 patients with functional menorrhagia, 1 with menorrhagia and dysmenorrhea, 3 with menometrorrhagia, 1 with premenstrual migraine, and 4 with painful breasts preceding the menses. The patients with *uterine bleeding* received *testosterone propionate* in 25 to 50 mg. injections 3 times weekly for 1 month, and those with *painful breasts*

and *migraine* were given injections only during the last 2 weeks of the cycle. Results with these patients were even more satisfactory than in a preceding series. Except for 1 patient with menometrorrhagia all were markedly benefited immediately following therapy. Bleeding was checked effectively, several patients having normal periods for the first time in 2 or 3 years. Breasts which ordinarily caused considerable pain produced little distress whether the trouble was due to simple engorgement or to adenosis. One of the patients, who received  $5\frac{1}{2}$  grains (350 mg.) during a month, showed a considerable degree of hirsutism and acne but no lowering of the voice.

From a practical standpoint, it is apparent that though moderate doses may frequently be effective, doses of at least  $4\frac{1}{2}$  to  $7\frac{1}{2}$  grains (300 to 500 mg.) throughout a period of a month are often necessary in menstrual disorders, especially in *menorrhagia* and somewhat less in mastopathies. It is quite probable that the obstacles to administering these large doses will soon be overcome with the progress now being made in the chemistry of androgens.

Caution should be exercised in administering testosterone propionate as it has already been demonstrated that virilism (hirsutism, change in voice and slight enlargement of the clitoris) can be induced in some women who receive large doses of this substance. Likewise, some women gain weight and develop an acne-form eruption. However, most of these disagreeable side effects disappear slowly after the hormone treatment is stopped, but some may persist for 6 months or longer.

**Biologic Effects of Androgen (Testosterone Propionate) in Women**—The effects of testosterone propionate were studied in a series of 25 women

with normal menstrual cycles by Geist, Salmon, Gaines and Walter.<sup>16</sup> Endometrial biopsies and vaginal smears were taken before, during and after administration of androgen.

Testosterone propionate in doses of  $7\frac{1}{2}$  grains (500 mg.) or more a month produced (a) temporary suppression of menstruation, (b) hypoplasia or atrophy of the endometrium and (c) evidence of estrogen deficiency in the vaginal smear. Restoration to normal occurred in all cases after cessation of treatment.

Doses of 3 grains (200 mg.) or less a month did not suppress menstruation or cause any demonstrable changes in the endometrium or vaginal smears. With intermediate doses the effects produced were variable.

Large doses of testosterone propionate (more than  $7\frac{1}{2}$  grains—500 mg.)—a month, the authors warn, may produce the following symptoms and signs: (a) Signs of estrogen deficiency, including temporary amenorrhea and senile vaginitis; and (b) androgenic effects, including hoarseness, hirsuties, acne and enlargement of the clitoris. In almost all cases these phenomena regress spontaneously after discontinuation of treatment.

It is suggested that the mechanism of testosterone action is threefold: (a) Inhibition of the gonadotropic factors of the hypophysis resulting in failure of ovulation and suppression of the normal formation of estrogen and progesterone; (b) direct inactivation of the available estrogens in the body, and (c) the production of androgenic effects (virilism).

### **Metromenorrhagia Treatment**

**With Testosterone Propionate—**The effects of testosterone on the endometrium are variable. Estrone will initiate and maintain rhythmic, intermittent contractility. Testosterone will inhibit this. Since the myometrium plays

such an essential rôle in controlling the volume flow of blood to the endometrium, the effect of testosterone on it becomes the more significant. Because intermittent, rhythmic motility is inhibited, the volume flow of blood to the uterus is lessened. By reason of its direct squeezing action on the myometrial elements, the volume flow of blood in the myometrium is reduced. The end result will be a reduction in the flow of blood to the endometrium, and thus, a diminution in the amount of uterine bleeding.

The immediate treatment of metromenorrhagia with testosterone propionate proved to be highly successful as reported by Sturgis, Abarbanel and Nader.<sup>22</sup>

The average minimal dosage required to lessen the bleeding materially varied from  $\frac{1}{6}$  to  $\frac{1}{2}$  grain (10 to 30 mg.). The total dosage necessary to stop the flow completely ranged from  $\frac{1}{6}$  to 2 grains (10 to 120 mg.), with an average of  $\frac{2}{3}$  to 1 grain (40 to 60 mg.). Two to 4 injections at intervals of 2 to 4 days were usually found sufficient. Injections should not be repeated during the transient exacerbation of bleeding which frequently occurs.

The only possible sign of defeminization ever observed was the loss of libido in 2 patients.

***Rationale for the Use of Testosterone Propionate in the Immediate Treatment of Excessive Uterine Bleeding***—The rationale for use of testosterone propionate in the immediate treatment of excessive uterine bleeding is presented by Abarbanel.<sup>23</sup>

All of the sexual hormones possess bisexual properties to varying degrees. Testosterone, in particular, is not only a powerful androgen, but also a very potent gynecogen. As regards the female, the effects exerted by testosterone

are dual, for it may behave as an estrogen or a progestogen.

A physiodynamic explanation is offered of the *modus operandi* by which excessive uterine bleeding is controlled by testosterone propionate. This interpretation is based, in main, upon the response of the myometrial elements to testosterone propionate.

Substantial anatomic evidence is presented to show clearly that the close structural interrelationship between the blood-vessels and the muscle fibers of the myometrium is such that adequate contraction of the myometrium will bring about a functional constriction of these vessels, especially the proximal (myometrial) portion of the spiral arterioles. Consequently, the volume of blood flowing to the endometrium, and thus, the amount of uterine bleeding, will be decidedly decreased.

The essential rôle played by the myometrial elements in controlling the amount of uterine bleeding now becomes manifest. It follows, then, that excessive uterine bleeding will occur if the proximal (myometrial) portion of the spiral arterioles fails to constrict, or be constricted, following the initial extravasation of blood distally. A basic cause, therefore, for excessive bleeding, regardless of the precipitating factor, be it myomas, subinvolution, pelvic inflammatory disease, or merely "functional," is a disruption in the normal hemodynamics of the uterine circulation accompanied by a disturbance in the pattern of uterine contractility at the time of menstruation.

The response of the myometrial elements to testosterone propionate is twofold: (1) First, this hormone will inhibit rhythmic, intermittent uterine contractions, thereby eliminating the pumping action of these movements. As a result, the volume of blood flowing to,

and thus through, the uterus will definitely decrease, for the degree of activity of muscle and its blood supply are directly proportional. (2) Second, the direct stimulative, squeezing effect of testosterone upon the myometrial elements will bring about a functional constriction of the myometrial vessels. The sum total of the twofold effects of testosterone propionate (inhibition of intermittent uterine contractions, direct stimulative action upon the myometrial elements) acting simultaneously upon the myometrial elements will result in a decided reduction in the flow of blood to the endometrium.

### Estrogens and Cancer

Gemmell and Jeffcoate<sup>17</sup> report that they have observed the appearance of carcinoma of the cervix in 3 patients among 43 who were treated with estrogens for kraurosis vulvae and senile vaginitis. The authors state:

The occurrence of these 3 cases cannot prove that carcinoma cervicis may be caused by estrogens, but they at least point out some practical lessons:

1. Every patient of menopausal or postmenopausal age, presenting symptoms of discharge, should be subjected to the most careful investigation to exclude carcinoma of the uterus, even when some lesion such as senile vaginitis appears to be the obvious cause.

2. Estrogens should be administered with caution if the patient has a lacerated or infected cervix or any other precancerous lesion.

3. Estrogens should probably not be administered to patients with a strong family history of malignant disease.

According to Lipschutz and Vargas,<sup>18</sup> the new synthetic estrogen diethylstilbestrol is far more active than the natural estrogens, estrone and estradiol, in the production of uterine and extrauterine fibroids in guinea-pigs. There is no

evidence, however, that it is more carcinogenic than these substances.

The relationship of ovarian hormones and female genital cancer is discussed by Allen.<sup>19</sup> The highest incidence of female genital cancer in aging persons at or after the menopause is well recognized. It is known also that ovulation usually stops after the menopause. Therefore a hormone imbalance at this time might well be an important factor in etiology of cancer of the genital organs in women.

One of the most important problems in the matter of aging is whether or not hormone therapy should attempt to extend the function of reproductive organs by administering ovarian hormones after the menopause; that is, in the absence of clearly established pathologic changes. Use of estrogens for severe climacteric symptoms, in senile atrophy and in other conditions is well known. Moderate use of threshold doses, if not continued too long, seems entirely logical in these cases. But after the demonstration that estrogenic treatment, long continued at high levels, is followed by abnormal growths of the female genital organs, including fibroid tumors of the uterus, cervical carcinoma and mammary cancer, Allen asks whether the clinician is justified in prescribing enormous doses of concentrated estrogenic preparations for aging women.

It may be pointed out, states this investigator, that in some cases aging women have already been given massive doses of estrogen without subsequent appearance of genital cancer. The answer to this lies in an understanding of cancer incidence. When groups of mice are injected with optimum doses of estrogen for induction of mammary cancer, only a certain percentage will die of cancer. Something of genetic susceptibility or resistance to cancer in mice is known,

for half a dozen generations can be bred in a year, but very little is known as yet of genetic susceptibility to cancer in human beings.

Allen points out therefore the possible danger of long-continued high levels of a hormone which is a natural constituent of the normal female body. These results also indicate that, unless an individual is especially susceptible, there are levels of estrogenic treatment which, so far as is known at present, are below the carcinogenic level. If therapeutic levels can be established within a safe range, the danger can be minimized.

**Cancer of the Breast Possibly Induced by Estrogenic Substance**—An interesting case of cancer of the breast possibly induced by estrogenic substance is reported by Auchincloss and Haagensen.<sup>20</sup>

The features of this case that make it valuable evidence concerning the possible carcinogenic effect of estrogenic substance are the following:

1. The patient had a familial predisposition to cancer, particularly cancer of the breast. Her father died of some form of internal cancer, while her mother had had breast cancer and a sister who had lost a breast was suspected of having had cancer.

2. The patient was given estrogenic substance over a relatively prolonged period—2 years and 3 months.

The patient received a relatively large amount of the hormone,  $1\frac{1}{4}$  grains (79.067 mg.) of estradiol benzoate (progynon B).

The carcinoma that did develop in the patient's left breast was of an unusual histologic type. It was accompanied by dilatation of ducts and epithelial proliferation throughout the whole breast, changes similar to those which the authors have observed in other human breasts following the administration of the estrogens.

The authors conclude that until more is known about the effect of the estrogens their use should be avoided:

1. In large or prolonged doses.
2. When there is a family history of breast cancer.
3. Without initial and repeated clinical examination of both breasts.
4. In patients with chronic mastitis, carcinoma or any form of breast neoplasm, either before or after surgical or radiation treatment.

### Excretion of Pregnandiol and Corpus Luteum

The excretion of pregnandiol only during corpus luteum activity is discussed by Cope.<sup>21</sup> Excision of the corpus luteum during early pregnancy results in a rapid fall to zero of the pregnandiol excretion, which normally continues in increasing amounts to full term. Pregnandiol is excreted during the luteal phase of the menstrual cycle, falls to zero before bleeding commences and is absent from the urine during the first or preovulatory half of the cycle. In contrast to this, no such excretion of pregnandiol occurred over a period of several weeks in 2 women suffering from secondary amenorrhea in whom it was unlikely that ovulation was occurring. No pregnandiol was excreted during 3 excessive uterine bleedings of a woman with a diagnosis of nonovulatory bleeding. This provides additional evidence of the close association between corpus luteum activity and pregnandiol excretion. The fact that the corpus luteum of pregnancy may be removed at the second or even the first month without abortion has led to the assumption that under these conditions the chorionic villi take over the hormone producing function of the corpus luteum.

Injection of progesterone to women not excreting any pregnandiol caused a

small but definite amount of the substance to appear in the urine. In view of this it is not justifiable to assume that the magnitude of pregnandiol excretion necessarily gives any quantitative indication of the rate of progesterone production by the corpus luteum. The state of the endometrium might prove an important factor in determining the percentage yield of pregnandiol from a given quantity of progesterone. However, pregnandiol excretion curves may reflect the state of the endometrium more closely than the activity of the corpus luteum. Until contrary evidence is had, it must be assumed that the observed pregnandiol excretion represents only a small proportion of the total endogenous progesterone production. Therefore it must be determined whether pregnandiol is the most important excretory product of endogenous progesterone. Available evidence does not reveal appreciable quantities of any substance in the urine other than pregnandiol glucuronide and allo-pregnandiol, probably also present as a glucuronide, which might be considered a breakdown product of progesterone metabolism.

The author concludes that hormone influences other than renal or hepatic and the metabolic state of the uterus and endometrium will prove to be important in progesterone metabolism and pregnandiol excretion.

### Pregnant Mare's Serum

Clinical experiences with equine gonadotropic hormone are reported by Erving, Sears and Rock.<sup>24</sup> Their study deals with a series of 48 cases of *sterility*, *dysfunctional flowing*, and *amenorrhea* treated with equine gonadotropic hormone. Sixteen patients were not ovulating, as proved by endometrial biopsy, and 9 others clinically were not ovulating. Twenty patients were ovulating, as shown

by biopsy, and 3 were clinically ovulating. Effects of treatment were judged in 12 cases by endometrial biopsy and by subsequent clinical course in the others.

Thirty-nine patients (81.2 per cent) were apparently unaffected by equine gonadotropic hormone. In no case was there any definite evidence of stimulation of ovulation by equine gonadotropic hormone. In the sterility group there was 1 pregnancy, but the authors feel it cannot be attributed to equine gonadotropic hormone. One other, an anovulatory patient, was found by biopsy to be ovulating 4 months after treatment. One patient with dysfunctional bleeding continued to flow for a month following equine gonadotropic hormone therapy and since then has had amenorrhea for 3 months. Six patients with amenorrhea stained or flowed after treatment, but none of these showed evidence of ovulation. Only 1 patient continued to flow at regular intervals. She seemed to be responding rather to thyroid than to equine gonadotropic hormone stimulation.

Allergic reactions to equine gonadotropic hormone appeared in 3 patients following therapy, and in 3 patients, a cyst of the ovary was noted following treatment.

**Pregnant Mare's Serum Hormone and Abnormal Ovaries**—Gray<sup>25</sup> studied the effect of pregnant mare's serum hormone in the form of "gonadogen" on the endometrium of 33 women with abnormal ovaries. Of 11 women complaining of amenorrhea, treated from 1 to 16 months, 8 menstruated, 7 regularly or fairly so. A gradually developing premenstrual secretory endometrium was observed in at least 4, 2 were apparently refractory and 2 women were insufficiently treated. Of 7 women with endometrial hyperplasia associated with metrorrhagia, a secretory endometrium

was obtained by 1 middle-aged woman. Only 1 of the 6 younger patients was clinically regulated. Of 7 women having interval nonsecretory endometria and metrorrhagia, slight secretion developed in 3 and a normal premenstrual endometrium in 1. Only 2 were clinically cured. Two patients with secretory endometrium and metrorrhagia were not improved. Six women, all with minor metrorrhagia but 1 in which no biopsies were taken, were improved or cured.

### Progesterone

Pregneninolone is a potent orally active progestational substance which produces both estrogenic and androgenic effects to a mild degree. It has been found definitely to cause suppression of the gonadotropic function of the anterior pituitary. Definite kidney damage was demonstrated in rats (chiefly in pregnancy) after administration of this preparation and therefore caution must be exercised in its use in the human being. When given to the intact pregnant rat, it produced abortion and stillbirths, and lactation was definitely impaired. In 31 per cent of cases studied by Cohen and Stein<sup>26</sup> the drug produced mild undesirable side effects, but these untoward reactions were seldom so severe as to necessitate withdrawal of the drug. *Pregneninolone* proved effective in approximately one-half of their patients complaining of *menometrorrhagia* but proved to be of little benefit of dysmenorrhea.

**Uterine Bleeding Induced by Progesterone**—Up to the present it has been assumed that the corpus luteum hormone (progesterone) is only able to produce bleeding of the uterine mucosa, provided that estrogenic hormone has previously been active in bringing about perfect proliferation of the mucous membrane. The present investigations re-

ported by Zondek, Rosin and Vesell,<sup>27</sup> make it clear that it is possible to induce bleeding during the intermenstrual stage (intracyclic bleeding) which takes place from an imperfectly proliferated mucous membrane (as has been verified by biopsy). It is, therefore, no prerequisite for the occurrence of a progesterone-produced bleeding that perfect proliferation be present.

These observations were applied in the treatment of amenorrheic women (*secondary amenorrhea*), and it became evident that to induce bleeding did not require preliminary treatment with estrogens. Seventeen out of 19 cases were successfully treated in this way. The presence of a certain degree of estrogenic hormone production is a prerequisite condition for the appearance of bleeding. This is clearly shown by the fact that in primary amenorrhea no result is obtained by treatment with progesterone alone. It is, however, also possible to induce bleeding in primary amenorrhea, provided that small amounts of estrogens are also given, previously to or simultaneously with progesterone.

It is interesting to note that during pregnancy even large doses of progesterone (up to  $2\frac{1}{2}$  grains—150 mg.)—are unable to produce bleeding, and it is, therefore, impossible to induce abortion in this way.

### The Sex Hormones

The sex hormones, their physiologic significance and use in practice are reviewed by Frank.<sup>28</sup>

The prepituitary hormones are of protein character and nothing in regard to their structure is known. The male and female sex hormones, as well as the adrenal androgen, belong to the steroid hormones, the molecular structures of which have been determined, and their close relationship to cholesterol shown.

The close chemical resemblance of the estrogenic, androgenic and adrenogenic substances to one another and to cholesterol is the mother substance and that the gonads and adrenal cortex utilize this primary substance to elaborate their specific secretions.

The average daily excretion of androgens is from 63 to 68 units for men and from 42 to 56 for women; of estrogens for men from 9 to 12 and for women from 18 to 36.

Frank notes that a permanent condition of chemical hermaphroditism persists throughout life in the human male and female. Disturbances in the ratio maleness to femaleness may perhaps give rise to clinical manifestations.

Absence, decrease or increase of the estrogens and/or of progestin causes functional disturbances in the female. Functional disturbances in the male, as yet not as well defined, are probably due to similar variations of androgen secretion.

The exact chemical constitution of active estrogens and androgens which occur in the circulation have not been fully clarified. Combinations, intermediate products and products in process of excretion have different potencies. These variations as yet defy analysis.

As to therapy in the female, estrogens are of use in the treatment of *infantile gonorrhea* and in almost every variety of *menopause* disturbance. Estrogens have been employed in many other conditions without convincing evidence of their efficacy. **Progestin** relieves *dysmenorrhea* and may *prevent abortion* due to defective function of the corpus luteum of pregnancy.

Androgens should prove effective in the relief of *castration symptoms in the male*.

Anterior pituitary-like gonadotropic factor is effective in causing the descent



of the testis in a large percentage of bilateral and unilateral *cryptorchid* patients.

When direct endocrine therapy is unavailing, improvement or cure may yet be obtained by other measures such as *snake venom*, *curettage* or *roentgen therapy* for *menorrhagia*; *protein diet*, *reduction of obesity*, or *thyroid extract* for *amenorrhea*.

### Stilbestrol

Clinical and experimental studies on the synthetic estrogen stilbestrol are reported by MacBryde, Freedman, Loeffel, and Castrodale.<sup>29</sup> This drug gave excellent subjective relief to 35 of 56 hypogonad women (62 per cent) and partial relief to 17 (30 per cent). It is a highly potent estrogen, producing estrous vaginal smears, proliferative changes in the endometrium, breast growth and all the other known effects of natural estrogens.

Compared to estrone, stilbestrol is approximately twice as potent when given intramuscularly. A milligram of stilbestrol orally is roundly equivalent to a milligram of estrone intramuscularly. By intramuscular injection, stilbestrol is approximately one-third to one-half as potent per milligram as estradiol benzoate. Stilbestrol is roughly from 50 to 66 per cent as potent orally as by injection.

Nine patients (16 per cent) had unpleasant effects, consisting of nausea in 5 instances and of nausea and vomiting in 4. In only 2 cases was it necessary to discontinue the drug. In no case were serious results detected. No abdominal distress, diarrhea or cutaneous rashes occurred.

Studies of liver function showed no evidence of hepatic impairment. No changes were noted in the blood or urine.

The effect of the synthetic estrogen upon lactation was studied in 315 par-

turient women by Abarbanel and Goodfriend.<sup>30</sup>

When administered orally soon after parturition in dosages up to 15 grains (1000 mg.) it did not inhibit the actual onset of lactation in the nursing human being. The appearance of the average normal amount of milk secretion, however, was delayed until as many as 5 or 6 days after the last dose of stilbestrol.

No effect at all was noted upon established lactation in the nursing human being with  $\frac{3}{4}$  to  $7\frac{1}{2}$  grains (50 to 500 mg.) of stilbestrol administered orally in divided doses over a period of 1 to 4 days.

In the prevention of painful engorgement of the breast in 65 non-nursing full-term mothers,  $\frac{2}{5}$  to  $\frac{2}{3}$  grain (25 to 40 mg.) of stilbestrol orally in divided doses failed to yield a satisfactory result in but 9, or 13.8 per cent. On the other hand, in a control group of 65 similar cases, 31 or 47.7 per cent, suffered from painful engorgement of the breasts.

In 35 cases where adequate established lactation had to be interrupted,  $\frac{4}{5}$  grain (50 mg.) of stilbestrol orally in divided doses provided satisfactory relief for painful engorgement within 24 hours in 30, or 85.7 per cent.

Of 25 primiparous nursing mothers given  $\frac{1}{12}$  grain (5 mg.) of stilbestrol daily for the first 3 post-partum days, practically painless and asymptomatic filling of the breasts occurred in 21, or 84 per cent. In the control group, however, only 5, or 20 per cent, had painless filling of the breasts. The pregnant and puerperal patient was found to be unusually tolerant of huge doses of stilbestrol.

Karnaky<sup>62</sup> has obtained most excellent results in *menorrhagia* by the use of stilbestrol. The patient is given 10 tablets of 5 mg. each and told to take 1 every night, beginning 2 or 3 days

before the expected period. The period is then missed altogether, is delayed and shorter, or else the patient will spot for 1 to 3 days. The blood loss is decreased 95 per cent. The cost of such therapy is about 72 cents. There are no injections and the patient need not come to the office. The same amount of male sex hormone would cost \$30 to \$35, and the results are far better with stilbestrol than with male sex hormone.

Stilbestrol in  $\frac{1}{4}$  to  $\frac{2}{5}$  grain (15 to 25 mg.) doses, Karnaky states, will stop menorrhagia in a shorter time than that required to take the patient to the hospital, prepare the operating room, and do a dilatation and curettage. He can keep a woman from menstruating or bleeding as long as he deems it necessary by giving  $\frac{1}{12}$  to  $\frac{1}{6}$  grain (5 to 10 mg.) of stilbestrol at night. No bleeding is produced when  $\frac{1}{12}$  grain (5 mg.) (125,000 I.U.) is given each day, but if drug is stopped there follows in 1 to 4 days a spotting lasting 1 to 8 days.

*Leiomyomas of the uterus and polyps of the endometrium* are also controlled by stilbestrol. One now can give  $\frac{1}{4}$  to  $\frac{2}{5}$  grain (15 to 25 mg.) and control the flooding from these sources, thereby saving an emergency operation as well as the loss of vital blood. When  $\frac{2}{5}$  grain (25 mg.) of stilbestrol is given, the follicles become hemorrhagic which may lead to moderate pains in the ovarian regions. In 12 cases of *incomplete abortion* bleeding stopped by the treatment employed in other uterine bleeding cases. Six cases of increased bleeding at delivery were checked by giving stilbestrol as outlined, states Karnaky.

### Subcutaneous Implantation of Hormones

Subcutaneous implantation of female and male hormone in tablet form in women is reported by Loeser.<sup>31</sup> The

author implanted female hormone tablets in 2 women and male hormone tablets in 10. The 2 women in whom estradiol tablets were implanted had theretofore been sterile. Both had infantile uteri, desired children, and had been treated unsuccessfully with female hormones and anterior pituitary lobe preparations. The result of the implantation was negative in the first patient, as the tablets were expelled 10 days after their insertion, being implanted too near the skin. The large quantity of estradiol in the second patient depressed the function of the anterior lobe of the pituitary. As a result, maturation of the ovum and menstruation did not occur. Local action of estradiol on the uterine muscle and mucous membrane of the uterus became visible. The uterus grew and the mucous membrane became converted into cystically proliferated endometrium and was cast off gradually by hemorrhage.

After the hormone tablets were removed the anterior lobe gradually recovered, the hibernating ovary was stimulated by fresh gonadotropic hormone produced in the anterior lobe, ripening of the ovum occurred again and hence there was normal menstruation. The muscular apparatus of the uterus had been substantially strengthened and was now able to draw up the semen, which it had previously been unable to do because of muscular deficiency. The patient became pregnant.

Of the 10 women given male hormone implants, 5 had uterine fibroids, 1 functional bleeding, 2 chronically recurring mastitis and multiple nodules in the breast, and 2 mammary cancer. The implantations controlled in some measure menorrhagia caused by fibroids in all the patients, and successfully in 3. Male hormone did not influence existing recurrences of breast carcinoma following an operation or Roentgen treatment.

## TRIPHENYLCHLOR- ETHYLENE

**Clinical Use**—Macpherson and Robertson<sup>32</sup> used triphenylchloroethylene in this investigation because its action is greater and more prolonged than that of triphenylethylene. The 41 cases treated included *amenorrhea*, *menopausal symptoms*, *atrophic vulvitis* or some similar condition, *atrophic rhinitis*, and cases in which it was desirable to *inhibit lactation*. Triphenylchloroethylene was prepared for oral use in tablet form, each tablet containing 3 grains (200 mg.); in ampoules containing 4 grains (250 mg.) dissolved in 75 minims (5 cc.) of sesame oil, suitable for injection, and in cocoa butter made up in the form of vaginal suppositories, each containing 1½ grains (100 mg.). Tablets are given after meals, and as many as 9 a day may be given without any fear of producing toxic effects. Two injections are given a week apart to begin with, followed by a third injection 3 weeks after the second. Subsequent injections may be given at intervals of 3 or 4 weeks according to the response produced. Vaginal suppositories are used nightly for 14 days of treatment and then on alternate nights or every third night, as determined by the progress made.

In each of the 4 cases of amenorrhea treated there have been periods of withdrawal bleeding between the course of treatment. The total dosage that has produced this result has been from 186 to 248 grains (12,000 to 16,000 mg.).

Of the patients with vulvitis and vaginitis, 7 had atrophic rather than primarily infective vulvitis and vaginitis. The eighth patient in this group complained of intense itching of the vulva. The drug was given orally in 4 cases and by injection in 4. The amounts used in each course of treatment were not con-

stant throughout this group, but the variations were not wide. The result of the treatment in almost every case was complete relief from symptoms and in 7 of 8 cases the local condition was obviously improved.

The patients with menopausal symptoms all received the drug in tablet form, from 3 to 27 grains (200 to 1800 mg.) (from 1 to 9 tablets) being taken daily for, in some cases, several successive courses of from 4 to 5 weeks. The effect of the drug was noticed within 2 days of the start of treatment, and after the average course, which lasted from 3 to 4 weeks, the action of the drug was maintained for another two weeks before any recurrence of symptoms was noticed.

Triphenylchloroethylene was given to 12 patients to inhibit or stop milk secretion, 6 by mouth and 6 by injection. In those treated by mouth the total dosage has been about 1 dram (4000 mg.) given over a period of 5 or 6 days. Where treatment was begun shortly after delivery, the breasts remained soft and painless in 4 of 6 cases. Of the other 2 patients, 1 experienced discomfort on the third day and the other secreted a considerable quantity of colostrum for 3 days but no milk. Of 2 patients, treated by injection on the first day of the puerperium, the breasts showed no engorgement and remained painless. Where lactation was already established, treatment by tablets or by injection of from 4 to 5 grains (250 to 300 mg.) led to cessation of milk secretion after from 3 to 5 days, and in no case was there any recurrence.

Trichloroethylene, the authors state, has no definite toxic effects and can be administered in large doses or over a long period. The duration of action by mouth closely approximates that of stilbestrol. By injection, however, the dura-

tion is singularly prolonged; after  $7\frac{1}{2}$  grains (500 mg), by the technic described, effective action persists for from 6 to 9 weeks. By this method, therefore, a very small dosage is sufficient to maintain a continuous high level of estrogen activity.

## LEUKORRHEA

The clinical and therapeutic aspects of leukorrhea are discussed by Bland and Rakoff.<sup>33</sup>

In arriving at an etiologic diagnosis the authors recommend the following procedures:

1. Fresh wet smear examination of the vaginal and cervical discharge. Dark field examinations are sometimes necessary.

2. Gram-stained smears. Occasionally special stains may be required.

3. Routine or special cultures.

4. Evaluation of the cellular content by smear methods as an indicator of estrogenic activity. Biopsy may also be employed.

5. Determination of the pH of the vaginal and cervical secretions, either with indicator papers or, preferably, with a pH meter.

6. Biopsy for histologic diagnosis.

**Cervical Infections**—In the acute stage of cervical infections the treatment is entirely along medical lines and is directed toward the rest of the infected tissues, local cleanliness and the establishment of proper drainage.

**Sulfonamide compounds** have yielded good results and have greatly reduced the time required for the treatment of acute gonorrhea.

In the chronic cervical infections topical applications of antiseptics and caustics to the cervix are of limited usefulness except when the infection is superficial. In the majority of cases the me-

chanical destruction of the infected area by the *actual cautery* is far more effective.

**Nonspecific Vaginitis**—In long-standing cervical infections, the continuous lowering of the vaginal acidity with the profuse alkaline cervical discharge may result in the displacement of the normal vaginal flora, which usually consists of gram-positive lactobacilli (Doderlein's bacilli), by a variety of other organisms. Not infrequently this results in a low grade nonspecific vaginitis. The associated leukorrhea may be controlled and the return of the normal flora hastened by the use of acid vaginal douches twice daily.

R. *Chlorothymolis* . . . . . gr. xx (13 Gm.)  
*Mentholis* . . . . . gr. xxx (20 Gm.)  
*Methylis salicylas* . . . . . f5ss (20 cc.)  
*Acidi lactici* . . . . . q.s. f5vi (1800 cc.)

Mix and label. A teaspoonful in 2 quarts of hot water, to be used as a vaginal douche morning and evening.

**Vaginal Trichomoniasis** Technically the steps of the local treatment which the authors carry out may be described as follows:

1. **Thorough exposure and cleansing** of the cervix, vagina and external genitals are essential. For this purpose, tincture of green soap, diluted 20 times with warm water, or a saturated solution of sodium perborate may be used. The latter has the advantage of effervescing when in contact with the tissues, thus aiding in the cleansing process. On the other hand, burns have occasionally been reported with the use of sodium perborate.

2. Any organisms within the cervical canal are destroyed by carrying an applicator dipped in a strong antiseptic solution, such as *tincture of iodine*, well into the structure.

3. The entire vaginal tract is thoroughly dried with soft cotton pledgets

or with a stream of warm air, following which the speculum may be removed.

4. A nonirritating aqueous antiseptic, such as *acriflavine* 1:1000, is introduced into the urethra with a medicine dropper. The introitus and external genitalia are then thoroughly dried with cotton or warm air.

5. Following the drying process an effective trichomonadicidal agent is applied to the vulvovaginal tract. The use of antiseptic powders in a drying base has been found especially effectual. Powders of this character may be insufflated by a vaginal powder blower.

A fine grade of *kaolin* is usually employed as a drying base and, in some instances, this alone may overcome the disorder. It is usually necessary to combine the kaolin with a protozoacide. The pentavalent arsenicals, such as *acetarsone* and *carbarsone*, are frequently used. *Sodium bicarbonate* may be added to these preparations to increase their solubility.

*Vaginal Powder with Protozoacide*

℞ *Acetarson. or carbarson.* . . . 1 part  
*Sodii bicarbonas* . . . . . 1 part  
*Kaolinum* . . . . .qs. 6 parts

Mix and label. 1¼ drams (5 Gm) to be insufflated into the vagina by the physician

*Silver picrate* 1 per cent, in *kaolin* is also highly recommended.

6. The foregoing treatment should be repeated daily for 3 successive days and then at intervals of 3 days until at least 6 treatments have been given.

7. Following the 3 initial treatments it is advantageous to have the patient employ a cleansing acid douche (prescription 1). From 2 to 4 quarts (2000 to 4000 cc.) of the solution at 105° F. (40.5° C.) should be used.

8. It is often necessary to continue daily vaginal douches during the menstrual period, since, as is well known,

many recurrences follow immediately or shortly after menstruation.

9. Vaginal suppositories medicated with various trichomonadicides are frequently used, but as a rule they simply control rather than overcome the infection. They are recommended as therapeutic adjuvants but not as curative agents.

10. The marital relation should not be practiced during the course of active therapy. Recurrence following coition calls for an examination of the husband to determine whether he is or is not harboring the parasite in the urethra or prostate.

11. After an initial course of treatment all local measures may be discontinued for several days, and the vaginal secretion during this time should be examined for the presence of trichomonads. No patient should be considered cured until she has passed through 3 or 4 menstrual periods wholly free from the organisms.

12. In resistant cases it is often necessary to treat the patient every second or third day through 2 or 3 menstrual cycles. In such instances one must carefully guard against cumulative toxic effects from the prolonged use of arsenicals, silver salts, picrates and the like. It is sometimes advisable to alternate treatment with several trichomonadicidal agents.

13. In pregnancy, active treatment may be indicated because of the severity of the symptoms or the "unhealthy" character of the vaginal secretion. In such instances it is best to begin treatment as warily as possible, and under no circumstances should intravaginal treatment be continued beyond the thirty-sixth week of gestation.

**Moniliasis**—In the treatment of moniliasis 3 objectives should be kept in view: First, prompt relief of the in-

tense pruritus; second, destruction of the causative organisms, and third, prevention of the spread of the infection to other surfaces, such as the surrounding glabrous skin or nipples or to the newborn, in whom it may cause oral thrush by contamination at the time of delivery.

These objectives may be obtained by first swabbing the entire lower genital tract and vaginal canal every second day with *sodium bicarbonate* (5 per cent) until all secretions and thrush patches are removed and then thoroughly painting the structures mentioned with an aqueous solution of *gentian violet* or solution of gentian violet plus *acriflavine*.

R *Gentiana violeta*, 1% aq. sol. . . 1 part  
*Acriflavina*, 0.1% aq. sol. . . . 1 part  
 Mix and label. Apply locally.

This solution does not stain as intensely and appears to be equally effective.

The solution is dried with a current of air from a hair drier or Sorenson pump while the speculum is still *in situ*. Although the relief afforded by the application of these solutions is prompt, they are objectionable to some patients because of staining of the bed linen and wearing apparel as they drain from the vaginal canal.

If the vulvar skin has become infected with the fungus, more persistent treatment is necessary. In addition to treating the vaginal infection, the cutaneous lesions must be diligently cared for by the application of *gentian violet in alcoholic solution* (5 per cent) or *tincture of iodine* (2 per cent).

**Leukorrhea in Children**—Treatment with *estrogens* is now accepted as a notable advance in the treatment of gonococcic vulvovaginitis. Although the hormone may be effectively administered in a number of forms, the use of

suppositories has proved to be the most convenient route and is accompanied by fewer undesirable effects.

A satisfactory technique which may be employed is as follows:

(a) The mother of the child is instructed simply to cleanse the vulva with soap and water.

(b) A small vaginal suppository, containing from 500 to 1000 international units of an estrogenic hormone is gently introduced into the vaginal canal at bed time. In the majority of instances the mother may be taught to do this.

In from 4 to 10 days a favorable response is generally noted in the vaginal smears, since large squamous epithelial cells replace the leukocytes and smaller cells as cornification occurs. The vaginal secretion becomes white and flaky and markedly acid in reaction. In this environment the gonococcus disappears. It is generally necessary to continue treatment for 4 to 6 weeks.

**Leukorrhea of Endocrine Origin**—*Hyperestrogenism* This type of leukorrhea is exceedingly difficult to treat. *Progesterone* from  $\frac{1}{30}$  to  $\frac{1}{2}$  grain (2 to 5 mg.) 2 times a week in the last 2 weeks of the cycle sometimes yields good results, while in other instances it may have little or no beneficial effect. An alkaline antipruritic douche is of palliative value.

A similar type of discharge may develop during the period in which large doses of estrogens are being administered for other purposes.

*Hypoestrogenism* Some atrophic changes in the vaginal epithelium are frequently seen in the postmenopausal period. For this condition *estrogen* is a specific therapeutic agent. This may be given parenterally, or, preferably, in the form of large vaginal suppositories. In the beginning, 1 suppository, containing from 2000 to 10,000 international

units of *estrone* or *estradiol*, may be inserted nightly.

## MENOPAUSE

### Artificial Menopause Produced by X-Rays

Since 1930 it has been the routine in some of the cancer clinics of this community to inactivate ovarian function by means of the roentgen ray in patients who have carcinoma of the breast before the menopause. The rationale of this therapy is to avoid possible stimulation of malignant breast epithelium by the ovarian hormones. Regression of osseous metastases has been noted following such treatment.

In this investigation by Nathanson, Rice and Meigs<sup>34</sup> studies of urinary excretion of the follicle-stimulating hormone (gonadotropic hormone, prolan A) and estrogenic substances were made at frequent intervals on the urine of 10 patients who were thus irradiated following radical mastectomy.

The authors conclude from their study that

1. The artificial menopause can be considered analogous to the spontaneous menopause, the major difference being the rate at which the climacteric is finally reached.

2. X-rays, if properly used with adequate-sized portals and dosage, are as efficient in producing the artificial menopause as surgery.

3. The success of castration with radiation depends to some extent upon the age of the patient. Larger doses should be employed to sterilize the younger group.

4. Assay of the urine for follicle-stimulating hormone and estrogenic substances and endometrial biopsies give valuable information as to the effective-

ness of radiation castration in the individual case.

5. Vasomotor symptoms of the climacteric are accompanied by hyperactivity of the anterior pituitary. Elevated levels of follicle-stimulating hormone may be found in the absence of vasomotor symptoms, but on the other hand elevations in follicle-stimulating hormone are almost always detected in the presence of these symptoms.

### Stilbestrol

The value of stilbestrol in the treatment of menopausal symptoms was studied by Payne and Muckle.<sup>35</sup> Stilbestrol was administered to a series of 68 patients suffering from menopausal symptoms. Forty-seven (69 per cent) obtained complete relief, 11 (16 per cent) partial relief, and 10 (15 per cent) were not relieved by the administration of the drug. Seven (10 per cent) of the patients developed nausea or vomiting. Based upon this modest number of observations, the authors gained the following impressions: Stilbestrol is estrogenic; and small quantities relieve climacteric symptoms rapidly and efficiently in the majority of patients. The most effective doses for this purpose range from  $\frac{1}{600}$  to  $\frac{1}{60}$  grain (0.1 to 1.0 mg.) per day. While a limited number of patients cannot tolerate stilbestrol, this intolerance appears to be manifested by minor gastrointestinal disturbances and not by major or permanent toxic effects, provided the dosage is restricted to the minimal effective requirements.

Mazer<sup>51</sup> states his observations on the use of stilbestrol in nearly 200 patients. The product has the physiologic attributes of the natural estrogens and has a potency of 5000 rat units per milligram. It is more potent when given orally than any other estrogenic substance. He found no changes in the weight, blood

pressure, basal metabolic rate, urine and blood constituents in 10 completely studied patients who received the product over a period of 3 months in relatively large doses. Cholesterol content of the blood rose to an abnormal height in 2 of the 10 patients. Nausea and vomiting followed the administration of large doses, such as  $\frac{1}{30}$  grain (2.0 mg.) daily, in about 25 per cent of the patients.

Experimentally, the administration of  $\frac{1}{60}$  grain (1.0 mg.) daily for 42 days produced no changes in any of the organs of the rabbit, but  $\frac{1}{20}$  grain (3.0 mg.) daily for 42 days produced definite necrotic changes in the liver, spleen and kidneys. In the rat  $\frac{1}{600}$  grain (0.1 mg.) daily for an equal length of time produced congestion of the vital organs, and  $\frac{1}{60}$  grain (1.0 mg.) daily produced definite necrotic changes in the liver, spleen and kidneys. Mazer points out that stilbestrol has a much higher toxicity than the natural estrogens when the dose is computed in terms of weight and not in terms of rat units.

Investigation by Israel<sup>61</sup> in 12 surgically castrated women indicate that as little as  $\frac{1}{600}$  grain (0.1 mg.) of stilbestrol taken orally twice daily maintains the blood level of estrogen at 1 M. U. per 40 cc., and the urine level at from 15 to 20 R. U. per 24-hour output in a castrated woman. This observation seems to support the viewpoint stressed by Payne and Muckle that small doses of stilbestrol are not only less toxic but clinically effective.

One hundred and twenty-five patients with surgical and natural menopause were treated by Von Haam, Hammel, Rardin and Schoene<sup>36</sup> from 2 weeks to 6 months with doses ranging up to 1 grain (60 mg.) of stilbestrol. In 75 per cent of the cases excellent or good results were obtained, with 39 per cent of the patients reporting better response

to this therapy than to any other estrogenic substance used previously. In 42 per cent of the patients some untoward symptoms appeared during the therapy. These, however, could be controlled in the majority of cases by reducing the dose, and the treatment had to be discontinued in only 9 cases.

Laboratory investigation of the function of the parenchymatous organs and of the erythropoietic system did not reveal any evidence of organic injury. A gastric analysis showed a slightly decreased response of the mucosa to the alcohol test meal after the administration of nauseating doses of the drug. Ten to 30 per cent of the ingested stilbestrol were excreted in the urine and feces during the first 10 days following its administration.

The authors feel that because of the ease of administration and the great economic advantages stilbestrol has a definite place in the treatment of the menopause provided that small doses are used and that the therapy is not continued over too long a time.

**Hepatotoxic Action** The alleged hepatotoxic action of stilbestrol was investigated by Freed, Rosenbaum and Soskin.<sup>37</sup> With the therapeutic doses ( $\frac{1}{60}$  grain—1 mg. daily) and the particular product which they used there was no evidence of any toxic action of stilbestrol on the livers of the menopausal women whom they treated. This was true even with doses of  $\frac{1}{12}$  to  $\frac{1}{6}$  grain (5 to 10 mg.) daily and in women who exhibited some liver dysfunction to begin with as judged by the bromsulphalein retention test. Furthermore, relatively huge doses of stilbestrol in rats and a dog did not give rise to gross or cellular pathologic conditions of liver or kidneys or to liver damage as judged by various criteria of hepatic function. Finally, a patient with indubitable liver damage



who was recovering from an attack of acute hepatitis was able to take 10 times the usual therapeutic dose of stilbestrol for a period of 3 weeks without the slightest evidence that his convalescence had been impeded.

The authors conclude that stilbestrol is not significantly toxic to the liver. They are unable to explain the gastrointestinal distress which follows the use of stilbestrol in some patients. Until this is explained it seems wise to discontinue the administration of stilbestrol in any patient who begins to complain of nausea or other side effects. Meanwhile, there seems to be little reason for withholding the use of a potent and convenient estrogen in such patients as do not experience these side effects.

## MENSTRUATION

Cyclic pulmonary edema associated with the menstrual periods of a young woman with advanced mitral stenosis is reported by Edeiken and Griffith.<sup>88</sup>

Repeated attacks of *pulmonary edema* occurred during 14 successive menstrual periods. *Mercupurin* given intravenously during an attack of pulmonary edema prevented subsequent attacks during that period. Injections of mercupurin intravenously, given before the menstrual period, prevented pulmonary edema during 3 periods, but a hacking cough and tightness of the chest occurred. The patient became entirely free from pulmonary symptoms following *irradiation of the pituitary gland* and has remained free to date (April 18, 1940), 10 months after irradiation.

## OVARY

### Acute Abdominal Conditions Following Ovulation

McSweeney and Wood<sup>89</sup> direct attention to the fact that (1) (a) ruptured

graafian follicle (2) a bleeding corpus luteum (3) a ruptured corpus haemorrhagicum and (4) a corpus haemorrhagicum cyst with or without rupture are conditions frequently overlooked in the differential diagnosis of acute lower abdominal pain in women. Ovulation may cause pain by rupture of the graafian follicle when the ovum is being extruded — the so-called "*mittelschmerz*" (midperiod pain), after the ovum has been expelled and the blood escapes through failure of the stigma to become sealed off. Later in the cycle there may be pain due to rupture of the corpus haemorrhagicum or to the formation of a corpus haemorrhagicum cyst, which may cause pain of itself or by its rupture.

A study of the records at the Boston City Hospital showed that, from 1926 through 1938, 257 patients were admitted with a chief complaint of abdominal pain due to ovulation or its sequels. Of these, 216 were operated on.

Three types of cases were differentiated. There were 74 cases, including 15 which were discharged without operation, which could be considered as cases of ruptured graafian follicle. The 59 cases in which operation was performed were characterized by absence of free blood in the peritoneal cavity and by evidence of recent ovulation. In this group nothing was done surgically to the ovaries. There were 165 cases of ruptured corpus haemorrhagicum, in 139 of which operation was performed. The latter showed evidence of free blood in the pelvis. The cases were treated by a mattress suture. In the third category there were 18 cases of corpus haemorrhagicum cyst, of which 13 had ruptured. Resection was done in all the cases of this group.

The authors studied the relative incidence of acute appendicitis and pain due to ovulation during 2 typical years

and found that there was 1 case with pain from ovulation to every 13 of appendicitis. In order to determine how frequently ovulation may cause abdominal discomfort not sufficiently severe to demand medical aid, the authors questioned for a month all gynecologic patients who had normal menstrual regularity and found that 21 of 134 patients, or about 1 in 6, frequently had abdominal pain of a minor degree midway between periods and that 53 of 134 patients (40 per cent) had some symptoms suggesting ovulation. Appendicitis and pain consequent to ovulatory phenomena may exist simultaneously. In cases in which the differentiation is not positive, a midline incision instead of a right rectus or McBurney's is suggested.

### Carcinoma

This paper by Pemberton<sup>40</sup> is an analysis of 149 cases of primary carcinoma of the ovary occurring among a total of 855 patients with ovarian tumors, excluding retention cysts, treated in the Free Hospital for Women and its private ward by the various members of the staff from 1906 to 1938.

The author uses Schiller's designation of adenopapillary carcinoma for these cystic types. They are subdivided into (1) serous and (2) pseudomucinous adenopapillary carcinomas, which appear to progress somewhat differently. Each of these is divided into (a) those which show a gross semisolid structure of adenomatous tissue in part or whole and (b) predominantly cystic ones. Finally, there are the medullary tumors.

The author believes that the uterus and both tubes and ovaries should be removed whenever possible, because bilateral growths occur so often and metastases are found frequently in the back of the uterus. It is often difficult and possibly useless to attempt this, however,

when the pelvis is filled with the growth and adherent omentum and intestine. The tumor should be removed intact, if possible, and tapping to decrease its size for easier removal should be reserved for elderly patients and poor risks.

When an operation for cancer of the ovary is done it would be wise to remove the omentum, regardless of whether or not gross metastases can be seen in it, because it is so often affected and may be the source of recurrences later.

One hundred and fourteen of these patients with adenopapillary carcinoma were treated more than 5 years ago and 37 lived 5 or more years after treatment (32 per cent). The semisolid tumors of both types are much more malignant than the cystic ones and the serous type more so than the pseudomucinous.

Pemberton believes that the peritoneoscope may be of value in the diagnosis of early cases, but finds it difficult to obtain a view of the bottom of the pelvis. Because such a large percentage (47 per cent) dies within the first 2 years after operation it might save a patient a useless operation and convalescence if she were not operated upon if the peritoneoscope showed generalized metastases throughout the abdomen.

### Low Dosage Irradiation

The effect of low dosage irradiation of the ovaries is reported by Rock, Bartlett, Gauld and Rutherford.<sup>41</sup> They used subcastrative doses of x-rays over the ovaries and pituitary in the treatment of 27 patients with menstrual disorders with or without sterility. Twenty-two had proved anovulatory flow or flow which was predominantly anovulatory with occasional ovulatory cycles. No endometrium was obtained on repeated efforts from 1 woman, and this

was presumed to be an instance of primary pituitary deficiency.

Five patients had cyclic ovulation but with associated disturbances: Sterility; polymenorrhea, or hypermenorrhea. None of these 5 patients was relieved or cured. Twelve of the patients with faulty ovulation were cured, and the treatment of 10 resulted in failure. If an ovulatory cycle could not be proved within 3 months after the completion of roentgen therapy the case was considered a failure.

Patients considered cured were those in whom biopsies demonstrated ovulatory cycles 3 months or more after roentgen therapy, those of sterility in which pregnancy proved ovulation or those who acquired after treatment the mola of menstruation with periodicity of characteristic flow. Three, or 13.6 per cent, of the patients became pregnant. The figures of cure are well above the most optimistic results reported from endocrine treatment alone. Many of the cured women were under endocrine treatment before roentgen therapy was tried. Regular ovulatory cycles began within from 2 to 10 weeks following the first roentgen treatment.

No apparent harm resulted when a subsequent series of treatments with the same dosage was given after an interval of from 2 or 3 months. Three doses, each from 50 to 60 roentgens, given over the ovaries seem harmless to the ovaries of women less than 35 years of age. Women older than this may suffer temporary or permanent cessation of follicular function. The authors believe that roentgen treatment of the pituitary offers no additional benefit. To explain the good results, they postulate a destruction by x-rays of persisting mature follicles, thus allowing a new cycle of follicle development and maturation.

### Struma Ovarii

Differential staining qualities of colloid and certain morphologic stigmata of the parenchyma leave little doubt that ovarian strumas are made up of aberrant thyroid tissue.

Casual statistics based on individual experiences place it at from 2 to 15 per cent of ovarian teratomas, mainly dermoids. Since the discovery of thyroid tissue in ovaries depends entirely upon a readily recognizable tissue mass or on good luck in making a microscopic search, small strumas may be easily overlooked. An ovarian struma (and not necessarily a very large one), under conditions yet unexplained, can seriously unbalance the metabolism of the body and at times invade other tissues through metastatic growth. According to existing reports, 8 strumas of the ovary have produced metastases, and a slightly larger number is described as having caused thyrotoxic symptoms. Emge<sup>42</sup> has encountered 2 instances of hyperthyroidism accompanying such tumors, 1 of which, in addition, produced extensive metastases. These are reported in detail.

Since these tumors consist of various quantities of thyroid tissue it is reasonable to presume that they function like the thyroid. Very little is known about this, partly because of their rarity and partly because they seem to reach a state of functional inactivity resembling, in certain respects, colloid goiters of the thyroid. Only occasionally is a tumor encountered which is active enough functionally to disturb metabolism, and unless such a tumor is large it can be overlooked.

Most strumas of the ovary are benign tumors with orderly growth habits. It is not known when they begin nor how long they grow. They are decidedly

commoner after the age of maturity. Although there are no reliable figures, about 5 to 6 per cent of these tumors may be expected to assume metastatic growth habits. There are now 9 such cases on record, including the one reported here. Metastases from an ovarian thyroid are not necessarily fatal. Only about one-half of the patients reported

health. Whether irradiation can arrest the growth of metastatic strumosis is conjectural.

The fact that some ovarian strumas can produce malignant metastases makes it imperative that careful study of the abdominal cavity be done at the time of operation and that bone surveys be made at least once a year thereafter.



Fig 1—Struma ovarii. Note large island of thyroid tissue in a state of early hyperplasia. (Emge: *Am. J. Obs. and Gyn.*)

died as a result of metastatic invasion. Contrary to the behavior of metastatic neoplasms of the thyroid gland, metastases from an ovarian thyroid are ordinarily confined to the abdominal viscera and are more often superficial than invasive. Bone metastases, which is more in line with the behavior of malignant thyroid tumors, have been reported twice.

The presence of metastases may or may not disturb the health of the host. The patient observed by the author, though still harboring a large amount of aberrant tissue, continues in good

### Tumor Classification

A modern practical and simplified classification of ovarian tumors is presented by Taylor.<sup>43</sup>

A classification based on histogenesis is recommended. The author believes that the ancient division into cystic and solid tumors should be abandoned. It is now evident, he states, that practically all varieties of ovarian neoplasm have benign and malignant counterparts so that this makes unnecessary the repetition of the entire list under both benign and malignant headings. His classification, he points out, represents the gen-

eral opinion of the time and is as follows:

**I. Dysfunctional Cysts of the Follicle and Corpus Luteum** — These represent disturbed ovarian function.

**II. Endometrial (Chocolate) Cysts and Endometriosis**—Since the origin of the disease is not agreed upon and may even lie outside of the ovary itself, the endometrial cysts must be given a special position as distinct from all of the definitely primary ovarian tumors.

**III. The Primary Tumors of the Ovary**—*A. The Epithelial Tumors*—These must be divided, of course, into 2 distinct types, (1) based on a "serous," and (2) on a "pseudomucinous" epithelium.

The Brenner tumor is perhaps best classified with this group. The presence in the tumor of mucous glands and its not infrequent concurrence with a pseudomucinous cyst suggest its close relationship. The Brenner tumor probably bears the same relationship to the pseudomucinous cystadenoma as that of another solid tumor, the serous cystadenoma. A vast simplification would follow the adoption of the terms, *pseudomucinous fibroadenoma* (Brenner) and *serous fibroadenoma* (Frankl).

*B. The Connective Tissue Tumors*—The *benign fibroma* of the ovary has maintained its classic position among ovarian tumors. The sarcoma, on the other hand, has all but disappeared.

*C. Teratomas* — (1) The common *cystic teratoma* or *dermoid*; (2) the *complex (solid) teratoma*. A special type of teratoma is the *struma ovarii*.

*D. Tumors of the Ovary Arising from Specific Cells*—For several years it has been common practice to associate 3 ovarian tumors together, namely (1) the granulosa cell tumor, (2) the ar-

rrhenoblastoma, and (3) the dysgerminoma.

1. *The Granulosa Cell Tumors*—The apparent importance of the granulosa cell tumors has steadily increased, as their frequency has become more evident. On account of its suggestive structure the folliculoid type was the first to attract attention, but recognition of various less definite forms having a cylindromatous, acinar, or even diffuse structure soon followed. To this basic group must now, tentatively at least, be assigned 2 somewhat more distinct forms, the "luteinized" granulosa cell tumor or "folliculoma lipidique" of Lecene (Moulonguet) and the theca cell tumor.

The degree of malignancy of the granulosa cell tumors has not been finally settled. In general they are probably less liable to lead to a fatal recurrence than are the common papillary cystadenocarcinomas.

2. *The arrhenoblastoma* has made itself known on account of the bizarre masculine changes which take place in the female constitution when such a tumor is growing.

3. *The dysgerminoma*, the third of the 3 special tumors, is of interest because of its morphologic identity with a tumor of the testis and because of its tendency to occur in pseudohermaphrodites.

*E. Tumors of Doubtful Status*—Of the first group may be mentioned the *endothelioma* or *perithelioma* which is perhaps on its way to the discard. Of the second group is the *menonephroma*, described recently by Schiller but still waiting to attain recognition. Finally there is the *hypernephroma* which for years has contended with the luteoma for a position among the ovarian tumors.

**IV. Metastatic Tumors.**

## SALPINGITIS

**Treatment—Hysterosalpingectomy** for chronic salpingitis is recommended by McDermott.<sup>44</sup> The author analyzed results in 60 patients from the Los Angeles County Hospital, all of whom had had bilateral salpingectomies for chronic salpingitis and later had to have hysterectomies. He believes that for every one of these there must be several who suffer from symptoms due to the "left-over uterus" but who are so discouraged by the poor results of their 1 operation that they refuse a second; or there must be those whose symptoms are not quite sufficient to justify another major procedure. The argument of the proponents of conservatism favoring the preservation of the child-bearing function is pertinent only when plastic operations on the tube or unilateral salpingectomy are performed.

The author believes that the chances of success are slight. The second argument, that of the physiologic value of the uterus, is met by the answers that the psychologic importance of menstruation is overestimated and that there is no proof that the uterus has an endocrine function, its only known purpose being that of child bearing. The argument of the technical difficulties of hysterectomy is refuted by the facts. To conserve an organ may or may not be conservative as far as the welfare of the patient is concerned.

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## STERILITY

An investigation of the vaginal smear and basal body temperature and its application to the study of functional sterility is described by Rubenstein.<sup>45</sup>

The author describes 8 types of epithelial cells which most accurately reflect the gonadal hormone production in vaginal smears. The vaginal mucosa of

children, old women and certain amenorrheic adult women is very thin and consists of basal layers of cells. These cells are characteristically round, somewhat larger than the large mononuclear leukocytes. In the nonpregnant woman they usually show various degrees of cornification. In the event of pregnancy the corpus luteum increases, and increasing amounts of theelin and progesterone are produced, in response to which cell types appear which may be used to diagnose pregnancy. Study of typical smears at various phases of the menstrual cycle shows that anovulatory cycles occur more frequently than heretofore supposed. The presence of infection or chronic irritation may invalidate the interpretation of vaginal smears and temperatures.

Usually the vaginal smear and basal rectal temperature will show a discrepancy when some gonadal influence affects one or the other; thus the combination of the 2 methods makes the other more reliable. The correlation between the temperature and gonad function is as follows:

During the phase of follicle development and increasing theelin production, the basal rectal temperature drops progressively. The low point is reached just before ovulation, when conception is most likely. The temperature rise continues after ovulation and should exceed 0.5° F. in the first 24 hours and 1° F. the first week. As soon as the corpus luteum has regressed (a few days premenstrually) new follicles begin to develop. Theelin production begins again, although at a low level. Since there is now no functional corpus luteum, the temperature depressing action of theelin is again apparent. The temperature drops progressively throughout the premenstrual phase of the cycle. In the event of pregnancy, corpus luteum

function persists and the postovulative temperature rise is maintained. If temperature curves of previous cycles are available it is sometimes possible to detect a pregnancy before the period is missed, as the temperature remains high. The temperature and smear techniques used together have proved to be as reliable in detecting early pregnancy as the Friedman test.

By use of the smear-temperature technique it has been possible to classify 3 varieties of functional sterility. The commonest type of functional sterility is that in which the cycles are anovulatory, in which smears show marked desquamation characteristic of ovulation with no clear-cut and sudden rise in temperature. Instead the temperature rises gradually. In the amenorrheic anovulatory cycle there is no rise in temperature and the smears persistently show typical cells.

A study of 739 cycles of 101 patients (66 of whom complained of sterility) showed that 338 seemed anovulatory; no patient was exempt from at least a single anovulatory cycle. Other causes of functional sterility are early abortion, failure of implantation and ovulation when coitus is avoided. In investigating functional sterility, attempts to determine the time of ovulation and any hormone deficiency in the preovulative or post-ovulative phase of the cycle and attempts to influence the cycle by appropriate therapy controlled by the vaginal smear-basal body temperature technic are indicated. If ovulation occurs, coitus is advised on the preovulative and ovulative days. If ovulation does not occur, therapy is directed to induce it.

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### URINARY TRACT INFECTIONS

There is experimental evidence that *sulfathiazole* will be as effective as sul-

fanilamide and sulfapyridine, if not more so, in the therapy of infections of the urinary tract. Helmholz<sup>46</sup> found that sulfathiazole had a bactericidal action on strains of *Streptococcus faecalis*, whereas sulfanilamide or sulfapyridine did not. Sulfathiazole also readily killed strains of *Bacillus proteus*. Neter<sup>47</sup> has confirmed the superior bacteriostatic action of sulfathiazole on *Streptococcus faecalis* (enterococci). Hill<sup>48</sup> concluded that sulfanilamide, sulfapyridine and sulfathiazole had an equal bacteriostatic action on strains of *Staphylococcus aureus*, *Streptococcus faecalis*, *Escherichia coli*, *Aerobacter aerogenes* and *Bacillus proteus*.

Twenty patients with infections of the urinary tract were treated by Spink and Hansen.<sup>49</sup> The drug was given a severe therapeutic test in some of these instances. Many of the patients had been treated unsuccessfully with other therapeutic agents, including sulfanilamide and sulfapyridine. Furthermore, some of the patients had partial obstruction of the urinary tract. The offending organisms included alpha hemolytic streptococcus (*faecalis* and *viridans*), *Staphylococcus albus* and *aureus*, *Bacillus proteus* and *Escherichia coli* infections of the urinary tract due to *Bacillus proteus* were most resistant to all forms of therapy. The dose of sulfathiazole used in these cases was 15 grains (1 Gm.) from 4 to 6 times a day for from 7 to 10 days. Definite clinical improvement was obtained in 13 of the 20 cases.

It may be of significance that the highest incidence of toxic reactions from sulfathiazole was in this group of patients with infections of the urinary tract. It would appear that sulfathiazole may have a definite place in the therapy of infections of the urinary tract, particularly infections due to staphylococci, alpha hemolytic streptococci, *Bacillus*

*proteus* and, in some instances, *Escherichia coli*.

The use of **sulfanilamide** and its derivatives in urology is discussed by Cook.<sup>50</sup>

In urology the actual presence of the drug in the urine in the free form undoubtedly is a factor in its effectiveness, and its presence in tissue fluids enables it to reach the deeper seated infections. More recently the bacteria-destroying property of the drug has been attributed to the accumulation of hydrogen peroxide due to the inactivation of catalase by the drug.

The sulfonamide compound may be given orally or parenterally. These drugs are almost entirely eliminated in the urine, partly in a free state and partly in a conjugated form, as an acetylated compound. It is the free form which exerts the bacteriostatic and bactericidal effect. When given orally the rate of absorption of these drugs varies with different cases and with the drug used, but usually 2 or 3 days are required to establish equilibrium between the amount ingested and the amount excreted. Somewhat less time seems to be necessary when **sulfapyridine** or **sulfathiazole** is administered. In certain instances oral ingestion is impossible for various reasons, and in these cases parenteral injection has been of great value. **Sulfanilamide** powder may be prepared in an 0.8 per cent solution in physiologic solution of sodium chloride and given subcutaneously. In this way a patient may be given more than 100 grains (6.5 Gm.) of the drug daily with little difficulty. The sodium salt of sulfapyridine may be given intravenously and some observers have recently shown that sulfathiazole may be given in the same way. The intravenous use of these drugs is useful in building up rapidly an appreciable level of the drug in the blood,

particularly for those patients who have difficulty in taking the drug by mouth. The disadvantage, however, is that while the concentration in the blood is built up rapidly it also decreases rapidly and frequent administrations are necessary if an adequate concentration is to be maintained.

Clinically, the author does not feel that determinations of the level of these compounds in the blood are necessary in the satisfactory handling of patients suffering with infections of the urinary tract. Many estimations have been made and only in rare instances has he seen concentrations more than from 5 to 6 mg. per 100 cc. with the dosage usually used. He believes that a greater concentration in the blood is rarely needed to destroy an existing infection.

In the field of infection of the urinary tract the oral and subcutaneous administrations are usually sufficient. Various dosage levels have been suggested by many observers. However, it has been his experience that in the majority of instances sulfanilamide and its more closely related derivatives need seldom be given in a dosage greater than 40 grains (2.6 Gm.) daily. This is given in equal doses 4 times a day. The ease of administration may be enhanced by supplementing each dose with a similar quantity of sodium bicarbonate. The addition of the latter drug may have an additional value in that Heimboltz and Sickler have shown that the efficacy of sulfanilamide in the urine is increased at a pH level of 7.5. If sulfanilamide must be given parenterally, a somewhat greater dosage is advised, as previously mentioned.

**Azosulfamide**, while not as effective as sulfanilamide in equal doses, is of great value in urologic work. It is given in a dosage of 60 grains (4 Gm.) daily and may have to be used over a somewhat



longer period. Usually sulfanilamide or azosulfamide is given for a period of from 8 to 14 days. At the end of that time we have deemed it advisable to stop the drug whether the urine has been sterilized or not. An intervening period of 2 or 3 weeks followed by a second course of the medication will frequently bring about the desired results. In a number of cases he has found a second and third course of the drug necessary before sterilization takes place.

More recently another derivative of sulfanilamide, namely *sulfathiazole*, has been added to our armamentarium. The original dosage used was 60 grains (4 Gm.) daily but recent work has led me to believe that in most cases 45 grains (3 Gm.) will be sufficient. This is given in divided doses by mouth and if it is at all nauseating its administration is likewise eased by giving it with milk. It has proved to be of inestimable value in the therapy of staphylococcic and gonococcic infections. In the latter condition Cook believes that 60 grains (4 Gm.) daily are advisable and I have continued this for a period of from 10 to 14 days, although in all his cases the discharge was stopped and the urine was clear in from 3 to 4 days.

In those cases in which the infection cannot be eradicated by chemotherapy, a thorough and complete search by a competent urologist should be advised because of the frequent association of complicating pathologic conditions such as stone, tumor, obstruction or cicatricial deformity.

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## UTERUS

### Dysfunctional Bleeding

The use of *testosterone propionate* in the treatment of premenopausal dysfunctional uterine bleeding was investigated by Mazer and Mazer.<sup>51</sup> The ad-

vantages of this form of therapy are: 1. It obviates the need of applying radium or the use of x-rays, which is usually followed by severe climacteric symptoms. 2. It does not cause sudden and permanent amenorrhea. 3. It does not require hospitalization and is therefore readily accepted by most patients.

The authors find that smaller doses, a total of from  $\frac{3}{4}$  to 3 grains (50 to 200 mg.) given over a month, are effective and do not evoke masculinizing changes. Testosterone propionate relieves dysfunctional uterine bleeding in about 50 per cent of the patients who submit to a month's treatment.

The *modus operandi* of the smaller doses in controlling uterine bleeding of the dysfunctional type is either through the ability of the product to neutralize the continuous action of estrogen on the mullerian tract or through inhibition of the unknown endometrial bleeding factor. Regardless of dosage, it cannot rejuvenate aging ovaries or stimulate the ovaries of younger women to biphasic activity; therefore its influence on dysfunctional uterine bleeding is temporary but long enough to permit natural readjustment to take place. Failure of readjustment results in recurrences.

The authors treated 64 women, 48 of premenopausal age and 16 younger women, with testosterone propionate in sesame oil given intramuscularly every other day for 1 month. Forty-four women received a total of from  $\frac{3}{4}$  to 3 grains (50 to 200 mg.) and 20 from  $4\frac{1}{2}$  to 9 grains (300 to 600 mg.). Thirty-five preliminary curettages were performed as an office procedure to eliminate malignant growths. The remaining women refused to submit to a curettage. A cure was considered to have been effected if the abnormal uterine bleeding ceased during the month of treatment and did not recur for at least 3 months

after its withdrawal. The follow-up period ranged from 3 to 19 months with an average of 7.6 months. Forty-two of the 64 patients (66 per cent) were cured and 22 (34 per cent) were not or were only temporarily improved. Twenty-seven or 77 per cent of the 35 women who were curetted remained well during the follow-up period, whereas only 15 of the 29 noncuretted patients remained well for this length of time. This indicates that in 25 per cent curettage alone arrested the dysfunctional uterine bleeding for a period of 3 or more months, at least long enough for the endocrine imbalance to adjust itself. This is in accord with the authors' experience with 82 metrorrhagic women who had received no other treatment than curettage.

Larger doses of testosterone did not yield better results; 14 noncuretted patients received the larger doses with a cure in 7, and 15 noncuretted patients received the smaller doses with a cure in 8. Seven of the 42 cured patients had recurrences of uterine bleeding in less than 6 months after withdrawal of treatment.

### Fundal Carcinoma

This study by Miller<sup>52</sup> is based on 183 patients with microscopically verified carcinoma of the body of the uterus seen in the Gynecological Tumor Conference at the University of Michigan Hospital since April, 1931.

The average time waste from onset of symptoms to beginning of treatment was approximately 11 months. This is an improvement when compared with previous reports on time waste.

Sixty-five per cent of patients in this series had commenced treatment before the fourth month after onset of symptoms.

(a) Histologic grading of endometrial carcinoma is only one of several factors helpful in determining prognosis.

(b) The author is impressed with the fact that histologic Grades I and II are particularly radioresistant.

Clinical grouping based on size of the uterus is practical. Our findings tend to bear out the general feeling that corpus carcinoma in a small or normal-sized uterus is associated with a somewhat better prognosis.

Methods of treatment and results are discussed and the following views expressed: (a) For inoperable cases of corpus carcinoma whether due to complicating illness or extent of disease, **x-ray therapy** followed by intracavitary **radium** is the procedure of choice. By this method they obtained 34.4 per cent 5-year survivors (37.0 per cent when corrected for noncarcinoma deaths). (b) For operable cases with possible exception of extremely early lesions they advise **preoperative irradiation** followed by **total hysterectomy** 6 weeks after completion of the radiation treatment. (c) X-rays are preferred to intracavitary radium for preoperative irradiation with surgery, they are able to report 70.5 per cent 5-year survivors (82.3 per cent when corrected for noncarcinoma deaths). (d) Radiation and surgery should not be looked upon as competitive forms of therapy but as remedial measures of proved value. Best results are obtained by using both in a supplementary manner.

Fibroids were found in 19.8 per cent of the cases. Miller cannot say that fibroids affect the prognosis.

Five patients had a double primary.

Metaplasia was common, occurring in 15 per cent. Its significance was not clear. It did not appear to affect prognosis.

Study of mortality revealed carcinoma as the cause of death in 71.1 per cent of 45 patients with complete data. Other causes included heart disease, pneumonia, embolism, intestinal obstruction, etc.

Primary operative mortality in 85 patients was 3.5 per cent (1 cardiac, 1 pneumonia, 1 peritonitis).

## VAGINA

### Trichomoniasis

The treatment of vaginal trichomoniasis is described by Karnaky.<sup>53</sup>

The vulva, vagina and perineum are gently washed with *vinegar water* (5 tablespoons in 2 quarts—liters—of water) and dried. From 1 to 2 drams (4 to 8 Gm.) of a hydroxyquinoline derivative (*floraquin powder*) are blown into the vagina or from 4 to 8 tablets of the preparation are inserted, encircling the cervix, with a small plug of cotton inserted at the introitus. The patient is instructed to insert 1 tablet every morning and evening for 12 days. Instructions are given that a douche should not be taken during this period. After 12 days vinegar water douches (5 tablespoons of vinegar to 2 quarts—liters—of water) are to be taken twice daily between and during the next 3 menstrual periods and up to the fourth menstrual period. At the end of the fourth menstrual period a fresh vaginal smear is made for *Trichomonas vaginalis* and if found negative the patient is pronounced cured. If the smear is positive the treatment is resumed.

Following each menstrual period for from 2 to 5 days 1 floraquin tablet is inserted morning and evening with vinegar douches as needed. Two tablets are inserted at the slightest itching or discharge and 1 tablet morning and evening for the next 6 days. The patient returns twice a week for observation.

For *trichomonas vaginalis*, pruritus vulvae or vaginitis with a great deal of tenderness from 1 to 2 drams (4 to 8 Gm.) of the powder are blown into the vagina every day until the soreness is gone. An acid jelly can be inserted twice a day as a home treatment. After the acute stage has subsided 1 tablet is inserted twice a day as a home treatment. In 400 cases of *trichomonas vaginalis* in private practice in more than 4000 charity cases at the Jefferson Davis Hospital, 94 per cent of the patients were cured by this method.

## VULVA

### Atrophy of Vulva

Atrophy of the vulva is described by Adair, Davis, and Schuitema.<sup>54</sup>

The physiologic atrophy of the vulvar structures predisposes to pathologic conditions. The atrophic skin is easily bruised as a result of minor trauma, coitus or irritating and infectious contacts.

Three distinct stages have been described in this disease. In the initial stage, the inflammatory symptoms predominate. The entire vulva is swollen, red, bruised and painful.

The second stage is chiefly characterized by the onset of atrophic changes. The skin of the vulva becomes indurated and thickened owing to increased thickness of the keratin layer. The usual elasticity disappears.

The final stage of the disease is the chronic stage, lasting years.

During the initial acute inflammatory stage of this disease it may be necessary to rule out other conditions which are associated with itching of the vulva.

Yeast vulvitis is one of the commonest infections which cause pruritus of the vulva. This condition is often associated with diabetes, so that urinalysis and a blood sugar determination will be of diagnostic importance.

Fungous infections are occasionally seen in the groins of women who complain of pruritus. Parasites such as pediculi or pinworms may likewise produce itching of the vulva. Neurodermatitis is a neurogenic lesion of the skin often associated with pruritus.

Carcinoma of the vulva may occur at any stage of chronic atrophic dermatitis of the vulva. It has been suggested that leukoplakic areas predispose to the development of malignant tumors.

**Surgical removal** of the vulva remains the most satisfactory treatment for patients who have marked evidence of the disease. If the lesion has extended around the anus to the posterior skin, it may be well to undertake the vulvectomy in 2 stages. During the first stage the vulvar skin proper can be removed. At a later date the skin posterior to the anus can be dissected away.

The operative procedure should take into consideration the blood supply to tissues. There should be no unusual pull on united skin edges, for these will become necrotic or heal poorly. Good mobilization of apposed surfaces will result in primary union. Rarely will any difficulty be encountered with the urethra, for a safe margin of normal mucosa is usually present.

Irradiation has been given up because it provided few, if any, cures. Occasionally temporary relief from the itching occurs, but the progressive cutaneous changes continue, and the danger of malignant disease will remain.

Endocrine therapy with *estrogen* has gained in popularity in the last few years.

### Cancer of Vulva

An analysis of 155 cases (1911-1940) of cancer of the vulva is presented by Taussig.<sup>55</sup>

The author emphasizes that early recognition and prompt adequate treatment

are extremely rare in cancer of the vulva. In spite of this the disease, because of its relatively slow growth, offers a reasonably good prognosis. Prevention of carcinoma of the vulva by **early excision** of the leukoplakic vulva should materially lower the incidence of the disease. Radiologic treatment of the disease gives disappointing results and is usually attended by painful burns.

The complete modified **Basset operation** gives splendid results in patients with operable lesions (Clinical Groups I-III) who are under 65 years of age. In older patients only those in better than average physical condition with relatively early lesions should be subjected to this procedure.

Approximately two thirds of the cases of cancer of the vulva are still operable at the first examination. In those in whom a Basset operation is done we can expect a 5-year survival in about 3 out of 5 (58.5 per cent), even though 2 out of 5 (41 per cent) already show evidence of lymph gland metastasis.

### Granulomas

Venereal and nonvenereal granulomas of the vulva are discussed by von Hamm,<sup>56</sup> based on a study of 155 cases.

Granulomas are circumscribed masses of granulation tissue formed in the course of the productive phase of inflammation. They are most logically classified according to their etiologic factor, which in the majority of cases is an infectious agent. The author stresses a subdivision of pudendal lesions according to venereal and nonvenereal infections as highly desirable since it emphasizes the fundamental difference in the diagnostic aspects of the 2 groups.

**A. The Venereal Granulomas — I. Syphilis**—Syphilitic granulomas may appear in any stage of the infection, although they are most common in the

second stage of the disease. The diagnosis of spirochete-negative granulomas rests principally on the biopsy, which usually can be easily secured. The

marked predominance of plasma cells, the perivascular type of infiltration and the intimal proliferation of the smaller and middle-sized vessels, together with



Fig. 2—*A* and *B* show epidermal carcinoma of the vulva on a basis of leukoplakic vulvitis; *C*, case of periurethral carcinoma; *D*, vestibular carcinoma on a syphilitic basis. (Taussig: *Am. J. Obst. and Gynec.*)

the evidence of many newly formed capillaries, are characteristic of this disease.

**II. Gonorrhea**—This infection is of little importance as an etiologic factor of

and spread often over the labia majora and the perineum, originate frequently as a consequence of the irritative character of gonorrheal discharge. They are not



Fig. 3—*A* and *B* are examples of carcinoma of Bartholin's gland; *C* and *D* are cases of primary carcinoma of the glans clitoris. (Taussig: Am. J. Obst. and Gynec.)

vulval granulomas since the thickly coated mucous membrane of the vulva is very resistant to the invasion of the organisms. Pointed condylomas, which are found in the moist parts of the vulva

specific for this infection. They are usually painful and may grow into immense cauliflower-like masses. The histologic picture shows a marked hyperplasia of the epithelium which grows on a scanty

stroma with a rich network of capillaries. A few foci of round cell infiltration can be noted. The epithelium is usually edematous and lacks keratinization.

**III. Chancroid** — The Ducrey bacillus is responsible more frequently for acute ulcerations of the vulva than for granulomatous lesions. The histologic picture of chancroidal ulcerations is charac-



Fig. 4—*A*, Group I carcinoma of the vulva; *B*, Group II infiltrating carcinoma of the vulva; *C*, Group II epidermoid cancer of the prepuce; *D*, Group III cancer of the left labia (Taussig: Am. J. Obst. and Gynec.)

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first patient was operated on 7 years ago, the most recent 1 year ago. The process continued to spread in 2 instances. This necessitated a second operation. An intra-epithelial epithelioma was found in 1 case. One patient had complete relief for almost 2 years when a reddish discoloration of the skin about the vagina and rectum appeared and an intermittent pruritus returned. A culture showed an abundant yeast growth and it has been very difficult to control the pruritus. In the only negro woman of the series 2 years after operation there was complete loss of pigment of the skin about the rectum. There were no subjective symptoms. A biopsy of this area showed hyperkeratosis and absent rete pegs and fibrosis, collagenous changes and lymphocytic infiltration in the corium. The basal pigment layers stopped abruptly at the border of the lesion. The pruritus returned 1 year after operation in another case. There were no fissures or leukoplakic plaques. Cultures were negative for yeast or fungi. A biopsy showed, chiefly, hyalinization of the corium, atrophy of the rete and some dyskeratosis. There were no complications in the remaining case. The complications in 4 of the cases were treated by applications of an ointment, suggested by Foss, containing 1800 rat units per gram of *estrogen* and 15 mg. of crystals.

### Pruritus

#### Treatment of Anogenital Pruritus

—This is discussed by Stillmans.<sup>58</sup> A large percentage of the commonest form of pruritus — that about the anus—is due to the slight film of fecal matter left after the use of dry paper for cleansing. The cases can be relieved by the use of toilet paper or cloth wet with water or *boric acid solution* after preliminary cleansing with dry paper.

The addition of 1 per cent saponated solution of *cresol* or of 10 to 100 per cent solution of *coal tar* may succeed, or it may be necessary to use these antipruritics only occasionally. They are more generally acceptable than ointments.

If the skin is dry and fissured, ointments may be indicated. *Zinc oxide ointment* containing 1 per cent of *phenol* or from 10 to 25 per cent *camphorated phenol* may be used, or ointment of *ammoniated mercury* with or without the same antipruritics.

One source of acute dermatitis about the anus and genitalia is the use of anesthetic ointments, procaine hydrochloride or related drugs. Ethyl aminobenzoate, orthoform and the newer proprietary anesthetics, as well as resorcinol, used because of a real pruritus without inflammation, sometimes result in a sharp, often weeping, dermatitis which causes intense suffering and may be the beginning of a widespread inflammation of the skin.

*Psychotherapy* can cure some of the anogenital cases, especially in women. There are reports of such cases that have been proved to be due to fear of another pregnancy after a difficult delivery, fear of pregnancy in the unmarried, masturbation or other forms of sexual maladjustment.

In the baffling cases sometimes seen, one may use the *injection of alcohol*, originated by Stone in 1916. The area involved must be carefully mapped out, with special attention to the border areas, which the patient may have neglected to mention. Then the vulvar and perianal regions are cleansed as for other surgery, a general anesthetic is administered, and 95 per cent alcohol is injected, the needle entering perpendicularly into the skin. From 2 to 4 minims (0.12 to 0.25 cc.) are injected just under the skin at

each point, the points being about one-fourth inch apart. In older patients these points must be farther apart to avoid sloughing. This procedure succeeds in most cases in relieving itching for from several months to several years. It can be repeated if necessary. Blood-vessels must be avoided.

Surgical excision for pruritus is to be used only in extreme cases as it often fails to cure.

### Tumors of the Vulva

Benign and malignant tumors of the vulva are discussed by Folsome.<sup>59</sup> The author believes that a better general understanding of benign tumors of the vulva is an important aspect of preventive gynecology and is essential for the proper insight and control of vulvar cancer.

In the group of *benign tumors* of connective tissue origin are the fibromas, leiomyofibromas, leiomyomas and lipomas. The rarer hemangiomas, lymphangiomas, neuromas and enchondromas are mentioned merely to complete the list.

Benign tumors of the vulva of epithelial origin include true papillomas and those papillomas commonly termed condylomas, arising from residual pathologic irritation of subacute or chronic infections such as gonorrhea, hidradenomas or sweat-gland adenomas of the vulva; supernumerary vulvar breast, which occasionally undergoes carcinomatous change; endometriosis, and the many varieties of cystic tumors of the vulva.

*Sarcoma* of the vulva is rare. It may develop in the vulvar end of the round ligament or may be primary in the vulva. Metastatic malignant tumors of the vulva are rare. Primary melanoma of the vulva has an appropriate incidence of 1 case to each 125,000 pelvic examinations.

*Basal cell carcinomas* of the vulva are relatively rare. Carcinoma of the vulva is

the commonest malignant neoplasm of the external female genitalia.

The author points out that metaplasia and malignant change in apparently innocuous vulvar tumors are inadequately emphasized. Papillomas, sebaceous cysts, pigmented moles, leiomyofibromas, vulvar breast tissue and sweat-gland adenomas are some of the benign vulvar tumors which may, at a later date in a woman's life, degenerate to vulvar malignancy.

Treatment and care of the patient presenting herself with a vulvar cancer are tending to become more rational in the light of present anatomicopathologic knowledge of vulvar cancers. *Vulval surgery combined with resection of superficial and deep inguinal lymph-nodes* continues to be the best treatment for *carcinoma* of the vulva.

By stressing periodic pelvic examinations, cancer educational programs may materially assist in preventing cancer of the vulva. By paying attention to simple lesions and the benign tumors of the vulva, the physician may prevent carcinoma of the vulva.

### Vulvovaginitis

The treatment of prepuberal vulvovaginitis with a new synthetic estrogen, *stilbestrol*, is reported by Russ and Collins.<sup>60</sup>

On diagnosis of gonorrheal vulvovaginitis the child, irrespective of age, weight, duration of symptoms or previous therapy, was given a  $\frac{1}{60}$  grain (1 mg.) tablet of diethylstilbestrol 3 times a day until 20 had been taken. The tablet was crushed and administered in 2 ounces (60 cc.) of milk. The usual prophylactic methods and instructions were given to the mother, but the only form of treatment given was orally administered diethylstilbestrol. In 22 cases negative smears for pus and gonococci were

obtained at the end of 7 days of treatment. Two cases required 9 days of treatment ( $\frac{3}{8}$  grain—27 mg.) and 18 days of treatment ( $\frac{3}{4}$  grain—54 mg.) respectively to produce a cure. The smear then showed only large cornified epithelial cells, some with pyknotic nuclei and mucus.

Within 72 to 96 hours the discharge changes in character, becoming thin, mucoid and white. The latter type of discharge persists throughout treatment, and complete disappearance of any type of discharge is noted within 1 or 2 weeks after discontinuance of treatment. The thick greenish yellow discharge definitely diminishes in amount within 36 to 48 hours.

In the first few cases treated some nausea and vomiting were noted, but these symptoms have not been observed since the drug was administered in milk. In no case did vaginal bleeding occur. In approximately two-thirds of the cases a darkening of the nipple and areola occurred, together with slight painless enlargement of the breasts. In several cases pigmentation and painless enlargement of the vulva also was noted. In all cases these symptoms disappeared within 3 weeks of discontinuance of the drug.

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## II. OBSTETRICS

### ABORTION

Treatment is discussed by Collins, Weed and Collins.<sup>1</sup> They employed *wheat germ oil* in the treatment of 36 cases of spontaneous, threatened or habitual abortion in combination with *progesterone* and/or *thyroid*. The daily maintenance dose ranged from 1 to 1½ drams (4 to 6 Gm.) unless the patient showed signs of threatened abortion, when from 8 to 12 drams (32 to 48 Gm.) were given during the first 24 hours and then they were placed on the daily maintenance dose. Oil was given until patients reached from 8 to 8½ calendar months of pregnancy.

Anterior pituitary-like gonadotropic substance in the form of *antuitrin S* was administered intramuscularly in 1 cc. doses given at weekly intervals until the patient was pregnant from 4 to 4½ calendar months. In a few cases injections were continued until the seventh calendar month.

One rabbit unit of *progesterone* was administered daily intramuscularly when cramping or bleeding was actually present and, when the symptoms ceased, antuitrin S was substituted.

*Thyroid extract* in from ¼<sub>10</sub> to ½ grain (0.0065 to 0.03 Gm.) doses twice daily was given to all patients showing evidence of hypothyroidism: Obesity; irregular menstrual periods, slow pulse and the like.

Cases were classified as "threatened abortion" if cramping pain in the lower part of the abdomen persisted longer than 24 hours or if a patient had bleeding and as "habitual abortion" if the patient had had 2 or more spontaneous abortions or had had one previous abortion immediately prior to or attempted to abort during her present pregnancy.

Of 24 patients with threatened abortion treated 3 went to completion despite therapy. Of the remainder, 14 have been delivered of normal, full term children, 1 has now passed the period of viability, and the remainder have retained their pregnancies without further signs or symptoms of abortion. This represents a successful arresting of the abortion in 87 per cent of these cases.

### Pregnandiol Determination

The pregnandiol excreted in the urine of 100 pregnant women with various

disorders was determined by Cope.<sup>2</sup> The author emphasizes the diagnostic value of this analysis

The important figure, he found, is not the concentration of pregnandiol but the total excretion in 24 hours. In the first few months of pregnancy, estimation of pregnandiol excretion can be of value in the diagnosis of pregnancy and its absence as evidence of a serious abnormality. Demonstration in a case of amenorrhea is strongly suggestive of pregnancy, for no other condition is so far known in which the 2 are associated. However, it must be certain that the pregnandiol excretion is not the normal prelude to an oncoming menstruation. To be of value, estimations must be capable of detecting as little as 3 mg. in the whole 24-hour output.

Absence of pregnandiol from the urine of a woman with signs or symptoms of threatened abortion is evidence of abnormality, and the determination should be repeated. If persistently absent, either abortion is inevitable, or the products of conception have been already partially or completely evacuated or the fetus has died without expulsion, *i. e.*, missed abortion. Distinction between these possibilities must be made by clinical means. Treatment of threatened abortion with no pregnandiol excretion is not complete until it is certain that the uterine contents have been evacuated.

As pregnandiol is believed to be derived from the placenta rather than the fetus, its excretion can be expected to continue when fragments of placental tissue are retained. In 1 of 6 cases of incomplete abortion with symptoms sufficient to require hospitalization, a doubtful trace of pregnandiol was found. Usually the retained fragments are either too small or too damaged to provide pregnandiol in recognizable amount. This may be influenced by the time

elapsed since abortion. When intra-uterine death is suspected on clinical grounds absence of pregnandiol from the urine supports the diagnosis, but the converse (as in incomplete abortion) is not always true. If fetal death is suspected and pregnandiol is found in the urine the estimation should be repeated at weekly intervals. A progressive fall is suggestive, and if the excretion falls to zero the evidence is almost conclusive. Pregnanndiol excretion provides information comparable to that of the Aschheim-Zondek and Friedman tests.

Chronic nephritis and toxemia of pregnancy may interfere with pregnandiol excretion. Deviations from the normal excretion in these conditions do not necessarily mean that the gestation is abnormal.

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## LABOR

### Asphyxia in the Fetus

The recognition and treatment of fetal heart arrhythmias due to anoxia are discussed by Lund.<sup>3</sup>

Variations of the fetal heart rate have long been ascribed to asphyxia and the recommended therapy has been immediate delivery. The early recognition of impending fetal asphyxia can be determined, the authors emphasize, by continuous or at least very frequent auscultation of the fetal heart sounds. Institution of specific therapy, **oxygen**, at this time will in many cases either partially or completely restore the fetal heart rate to normal and successfully combat the anoxia. The response to oxygen therapy should be noted within 10 minutes and frequently is apparent in less than 5 minutes. If after 15 minutes of therapy no improvement is noted, it may be assumed that oxygen will be of no value. The time of preparation of a patient for operative delivery is usually

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### Pregnandiol Determination

The pregnandiol excreted in the urine of 100 pregnant women with various

of the bladder has the main idea of preventing extension of the incision in the musculature of the uterine corpus when the lower segment was not well formed, or when delivering a large fetus.

**2. Transperitoneal Cervical Cesarean Section (Peritoneal Exclusion)**—This operation is known as the Veit-Fromme-Hirst procedure. Veit and Fromme of Halle, in 1908, proposed a method whereby an extraperi-

Peritoneal exclusion is recommended for the woman who had been long in labor, with or without ruptured membranes but with potential infection.

**3 Extraperitoneal Cesarean Section**—The extraperitoneal cesarean section is represented by the operation of Latzko. Advantage is taken of the loosening and raising of the peritoneal sac from the lower uterine segment after a long labor. This procedure is per-

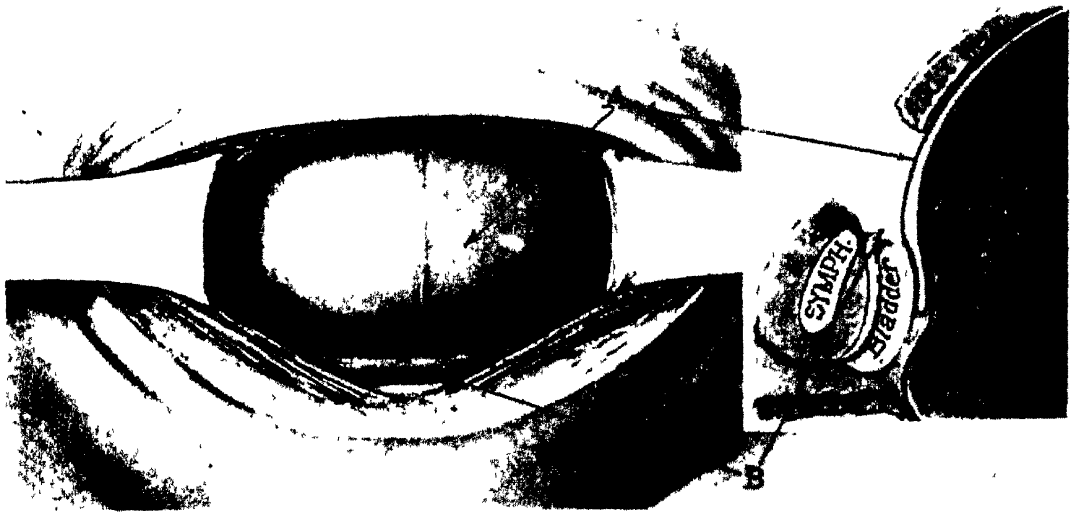


Fig. 2—Rectus muscles retracted laterally allow parietal peritoneum (A), fascia transversalis, and bladder (B) to balloon up, with urachus glistening in midline. (Smith Am. J. Obst. and Gynec.)

toneal space for delivery was created by uniting the layers of dissected visceral peritoneum to the parietal peritoneum by means of sutures or clamps, to protect the peritoneal cavity from the spill, and to leave the uterine incision outside of the general peritoneal cavity during the process of healing.

More recently Smith,<sup>5</sup> of New York, submitted a technic of peritoneal exclusion through a Pfannenstiel incision, and with a transverse incision in the lower segment in order to overcome one of the disadvantages of the Veit-Fromme-Hirst, namely the fixation of the lower uterine segment to the abdominal wall.

formed through a vertical abdominal incision, the intact peritoneal sac is raised upward from the bladder and the bladder is displaced laterally to the right. This clears a space in the lower segment which is ample for the placing of a longitudinal or vertical incision of sufficient length for delivery. This method, reserved for potentially or frankly infected women has replaced the radical or Porro cesarean section in a number of clinics. Waters substitutes a transverse incision for the longitudinal incision of the lower segment as used by Latzko.

Gottschalk-Portes operation, or temporary exteriorization of the uterus, has rendered important service in the ex-



hausted, badly infected patient. Its employment will always be necessarily limited.

**4. Transcervical Cesarean Section with Peritoneal Exclusion and Bladder Mobilization**—Smith<sup>5</sup> mentions

the abdominal scar and (3) abdominal adhesive bands. Smith, therefore, offers an interesting modification of this technic by moving the operation down from the original site to the safer lower uterine zone behind the bladder. He

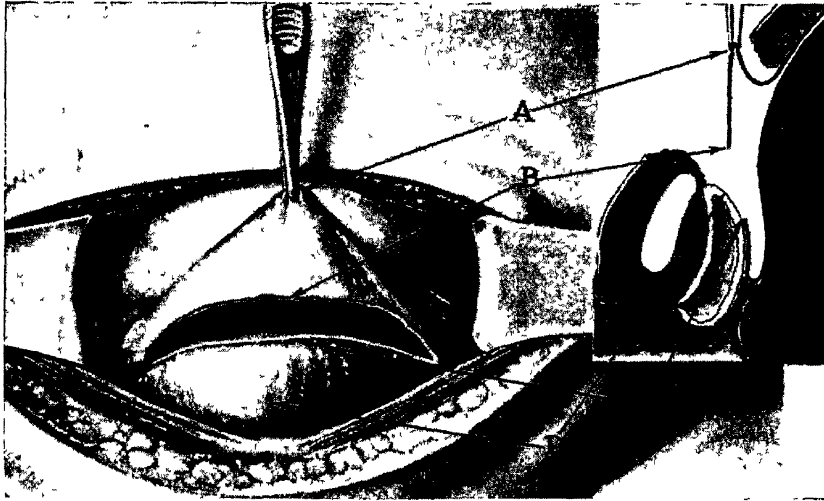


Fig. 3—Parietal peritoneum (A) opened at B—C, cutting transversalis fascia just over bladder (D). (Smith. Am J Obst. and Gynec)

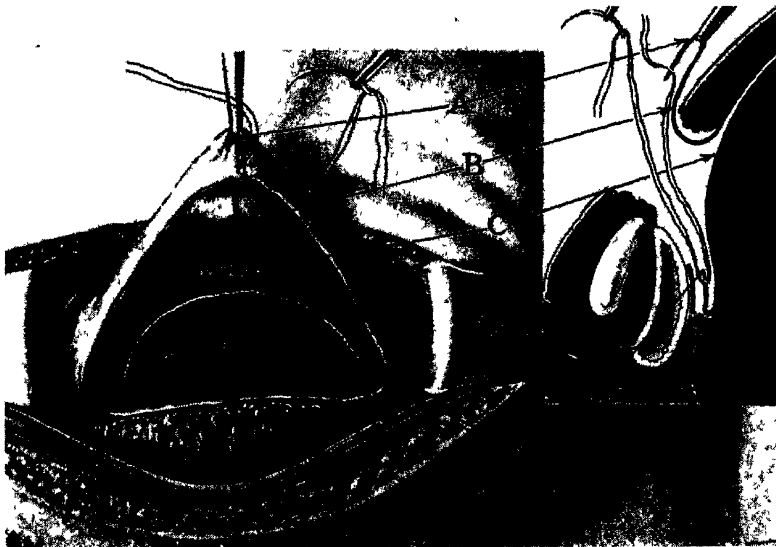


Fig. 4—Vesicouterine fold of peritoneum (D) opened transversely (as in low flap operation) and stitched to superior parietal peritoneum (A), to exclude peritoneal cavity (BC) (Smith: Am. J Obst and Gynec.)

3 definite objections to the Veit-Fromme-Hirst operation, *i. e.*, (1) fixation or facing of the uterus to the anterior abdominal wall, (2) endometriosis in

believes it is safer than either a classical or low flap operation.

**Technic**—A 4½-inch Pfannenstiel incision is made 1 inch above the sym-

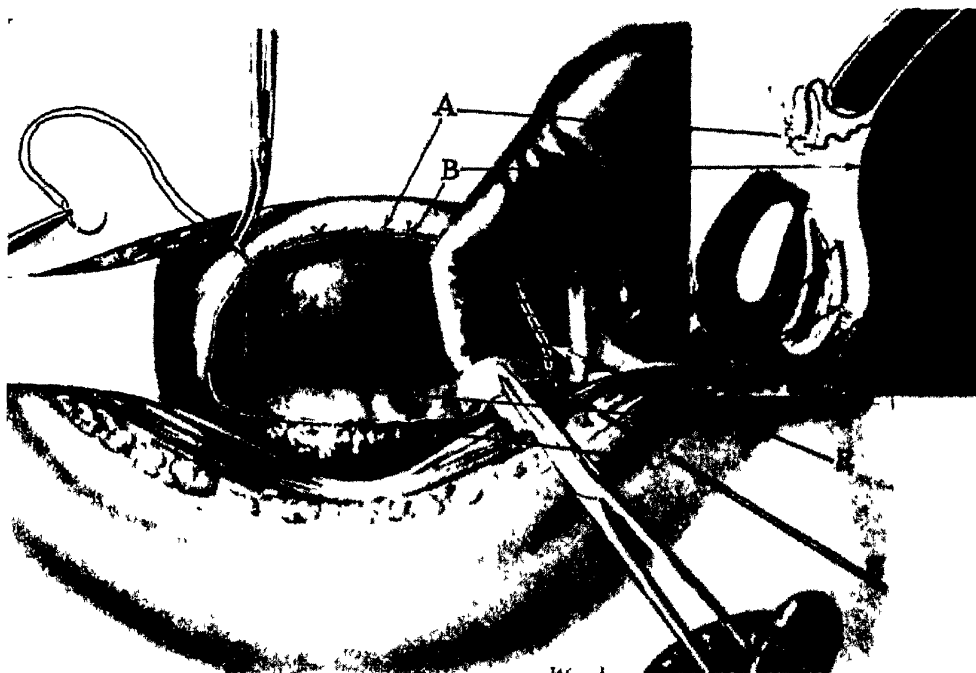


Fig. 5—Visceral peritoneal bridge, which varies in width (*C—D*) in different cases, being cut at closed apex of suture (*S*), after completed stitching of parietovisceral peritoneal layers (*HP*), which then excludes bilaterally and entirely peritoneal cavity from lower uterine segment (*B*). (The artist depicted scissors cutting too far towards midline, instead of at apex (*S*)). (Smith: Am. J. Obst. and Gynec)

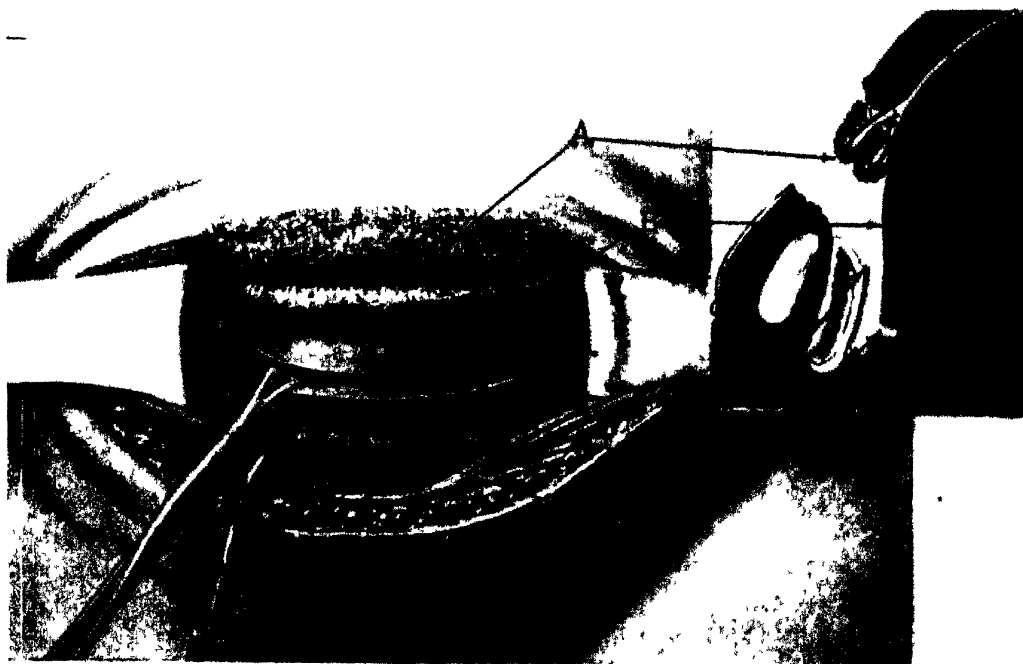


Fig. 6—Protective gauze strip (*A*) placed over parietovisceral peritoneum. Mobilized bladder (*D*), just before retractor hides it under symphysis. Lower uterine segment (*B*) above curved cervical incision (*C*). (Smith: Am. J. Obst. and Gynec)

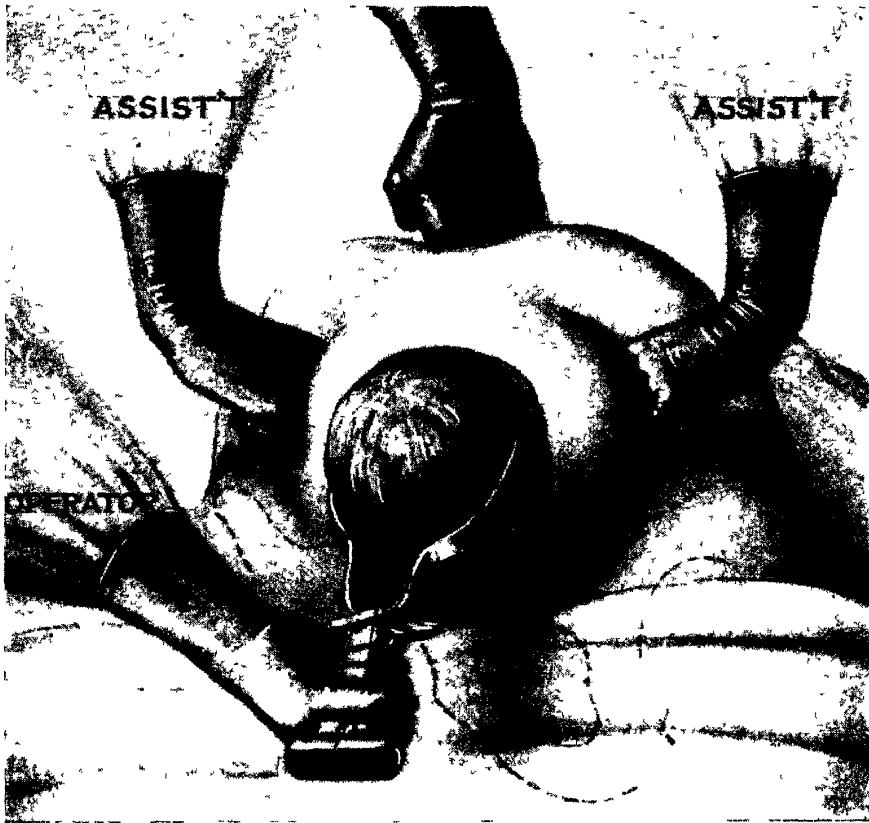


Fig. 7—After vertex is dislocated out of pelvis up into wound and forceps applied, fundal and lateral pressure facilitate extraction. (Smith: Am. J. Obst. and Gynec.)

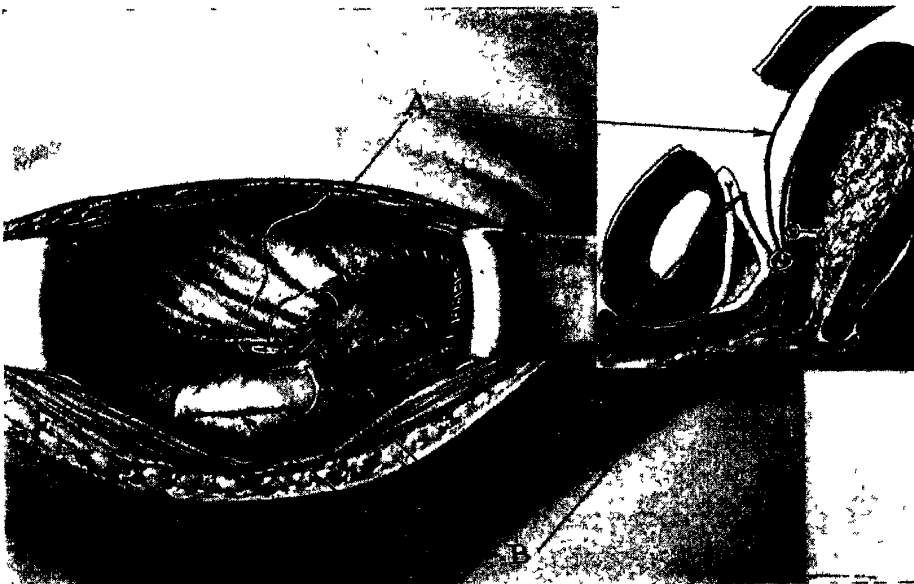


Fig. 8—Parietovisceral fold (A) brought down and stitched to bladder peritoneum (B), or to (C) if (BC) is too wide. (Smith: Am. J. Obst. and Gynec.)

physis pubis, down to the fascia. The illustrations depict the subsequent steps of operation.

According to the author the advantages of this operation are as follows:

3. It eliminates the possibility of subsequent intra-abdominal hernia.

4. It minimizes trauma to the bladder and preserves the nutrition of the peritoneum.

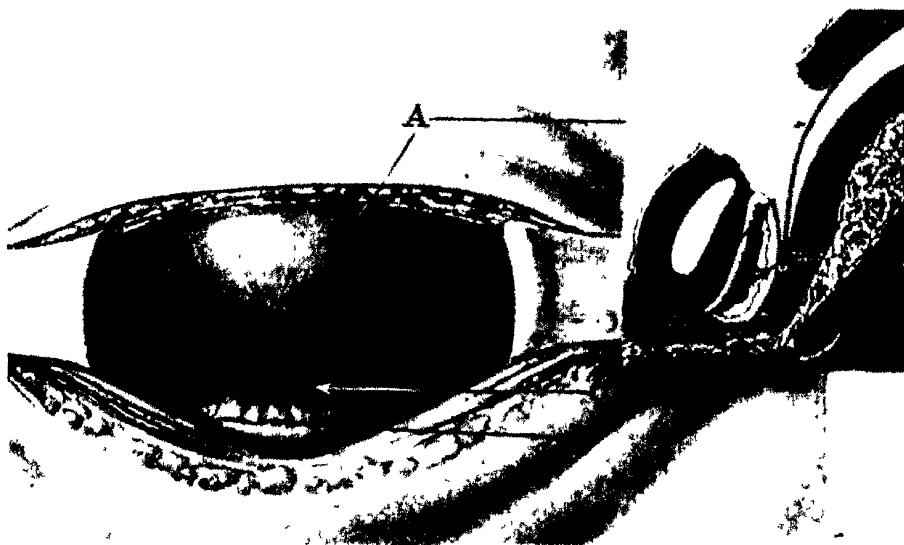


Fig. 9—In clean cases bladder (B) may be left unsutured or may be stitched to parietal peritoneum (A) without drainage. Insert shows uterine gauze packing. (Smith: Am. J. Obst. and Gynec.)

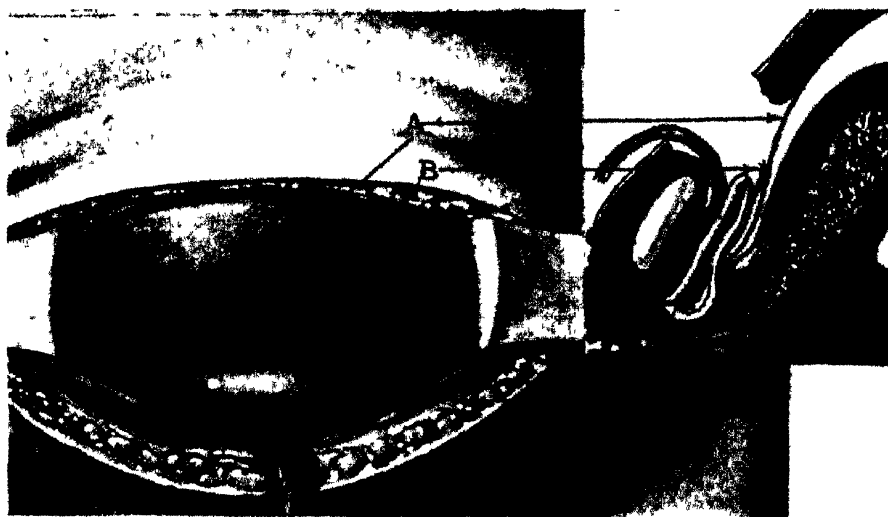


Fig. 10—In infected cases drainage may be instituted either suprapubically, as a space of Retzius drain, or preferably through a cervical puncture, as indicated in insert. (Smith: Am. J. Obst. and Gynec.)

1. It affords a more roomy elastic area than any of the other exclusion operations.

2. It precludes the formation of post-operative adhesive bands.

5. It localizes the operative site so that the ureters and bladder are not jeopardized.

6. It restricts the operation to the well-oriented lower peritoneal cavity,

yet provides complete peritoneal exclusion.

7. It is equally useful in infected and noninfected cases, and is not contraindicated by breech presentation, placenta previa, and other intrauterine complications.

### Dry Labor

Newer concepts of dry labor are presented by King.<sup>6</sup> A comprehensive survey of the literature since 1921 shows no evidence whatever to support the traditional belief that dry labor is "long, difficult and dangerous."

All available evidence drawn from deliberate experimental work, from the results of inductions and from various series of observations shows, on the contrary, that in dry labor (*a*) the duration is shorter, (*b*) there is no greater morbidity, (*c*) there is no greater incidence of interventions, (*d*) there is less damage to the cervix, (*e*) the fetal mortality is no greater and (*f*) there is no adverse effect on the psychologic or physical development of the child.

Dry labor should no longer be listed as a complication of parturition and may not be used as an excuse for operative intervention. The cause of dystocia in the presence of prematurely ruptured membranes must be sought for elsewhere.

The author concludes that the accumulated evidence controverts the theory of the hydrostatic wedge mechanism of the dilation of the cervix, which, although very pretty as a concept, has been doubted ever since its inception.

Offered originally in 1806 and revived within recent years, the explanation of dilatation by Dewees does not require the amniotic sac but depends on reciprocal muscular action only. This theory accurately coincides with clinical observation, does not confuse the picture

in certain cases of dystocia and should be more widely known.

### Hemorrhage

**Vitamin K**—Adequate administration of vitamin K to the mother before delivery appears to be the most rational method of treating prothrombin deficiency in the newborn and its administration may become as routine as the use of vitamins A and D earlier in pregnancy. Its administration either to the mother before delivery or to the newborn, Macpherson, McCallum, and Haultain<sup>7</sup> state, would appear to be especially indicated (1) in cases of maternal toxemia, (2) in premature labor, (3) in difficult or instrumental delivery, (4) when breast feeding is not possible, (5) when any cerebral symptoms develop during the first few days of life, (6) in cases of hemorrhagic diathesis, icterus gravis neonatorum and anemia and (7) when an operation is necessary on the newborn.

Macpherson and his associates estimated the prothrombin index in 54 infants during the first week of life. The principal feature was the extreme variation in the prothrombin index between different individuals on the same day and in the same case on different days. An appreciable decrease from the cord estimation was often demonstrated within 24 hours and this fall continued, reaching its lowest value from 36 to 84 hours post partum.

About the fifth day post partum the prothrombin level rose sharply and became stabilized at about 75 per cent. It gradually rose over a period of months. A vitamin K analogue was given in the early neonatal period to 36 babies. The administration to 20 infants within 24 hours of birth raised the prothrombin index to from 80 to 90 per cent and

stabilized it at that level during the first few days of life. Thirty-one mothers were given a vitamin K analogue ante partum. The effect on the prothrombin index of the infant during the first week of life was qualitatively identical with that obtained by giving the same substances directly to the baby during the first 24 hours of life. There is no advantage in giving more than 50 mg. by mouth to mothers.

The maximal effect will be obtained in the newborn if an adequate dose is given to the mother between 12 and 4 hours before delivery. The contents of the intestine are sterile in the newborn. Therefore, enough vitamin K cannot be absorbed until bacterial invasion of the bowel occurs. Breast feeding or the use of unsterilized breast milk on the first day should assist this synthesis by supplying numerous harmless bacteria, but this does not afford any protection against the fall in plasma prothrombin.

### Malpositions

A study of the *occipitoposterior positions of the vertex* based on an analysis of 106 consecutive cases is reported by Proctor and Dickinson.<sup>8</sup> The etiology of occipitoposterior positions is dependent on the presence of abnormally directed forces during labor. This in turn is most often caused by the presence of some pelvic disproportion—usually of the simple flat variety.

In treatment there are 3 cardinal principles: Awaiting dilatation; awaiting engagement and awaiting rotation. The first 2 are fundamental in delivery from below, but the last, if not spontaneous in a reasonable time, should be accomplished manually for the welfare of both mother and baby.

From statistics on 106 consecutive cases of occipitoposterior positions the following facts seem most evident:

Parity and age are not factors in the complication.

A previous history of difficult labor is frequent but not decisive, since the size of the fetus is a variable.

Most of the patients in whom pelvic measurements were possible presented evidence of moderate shortening of the true conjugate. This was true also for the intertuberous measurement.

Long labor and increased loss of blood are frequent, although, when the baby is small, the reverse may be true. The ill fit of the fetal head at the pelvic brim often leads to premature rupture of the membranes. Maternal morbidity was somewhat higher in this group.

### The Use of Solution of Posterior Pituitary

DeLee<sup>9</sup> states that proprietaries such as thymophysin, thyuitary, pituthymin and combinations with quinine are not to be recommended. They are diluted solution of posterior pituitary or are the drug disguised. Even natural labor can cause damage and/or death to both mother and baby.

Solution of posterior pituitary augments the forces of labor which inflict such damage and/or death—lacerations of the cervix, vagina, perineum, even rupture of the uterus, and cerebral damage in the babies.

Solution of posterior pituitary may cause severe shock and anaphylaxis and may explain certain fatalities in dysrhythmisms and circulatory and renal diseases. The medicolegal aspects of administering a potent and dangerous drug, as a matter of convenience, are worth consideration.

Proper indications for solution of posterior pituitary are numerous: in pregnancy to induce labor, in labor, and postpartum. These indications are well defined and defensible.

In more than 100 cases Murphy<sup>46</sup> has recorded with the Lorand toco-graph the character of the uterine movements initiated by the hypodermic administration of solution of posterior pituitary at term and during labor. These observations show that optimal doses either initiate or reinforce rhythmic uterine contractions, whereas overdosage almost invariably induces tetanic spasm. The latter may last for many minutes before good quality rhythmic contractions begin. At the University Hospital recently a patient was ordered 1 minim (0.06 cc.) of pitocin; by mistake she received 16 minims (1 cc.). She experienced a uterine spasm which lasted 33 minutes. He has found that, if tetanic spasm is to be avoided, the optimal dose is in the neighborhood of 1 minim (0.06 cc.). Such a dose is effective for about 30 minutes and can be repeated safely at that interval as often as indicated by the condition of the patient. For accuracy in dosage he has found most suitable a 0.25-cc. syringe. With this, one is not so likely to give an overdose as when employing the usual 1-cc. tuberculin syringe or the 2-cc. syringe.

Solution of posterior pituitary Douglas states, has a place in the treatment of certain patients in labor, but only when a nontetanzing dose is employed and that dose is in the neighborhood of 1 or 2 minims (0.06 to 0.12 cc.).

The use of solution of posterior pituitary to accentuate the pains of normal labor and to hasten delivery is to be condemned, according to the investigations of Sharkey.<sup>10</sup> Solution of posterior pituitary may be used with care and discrimination.

(a) In certain cases of true primary uterine inertia after having satisfied oneself that no mechanical hindrance to delivery is present.

(b) In lieu of low forceps to terminate labor when the second stage is unusually long because of weak pains and there are no facilities to deliver by forceps

(c) In abruption placentae by those who possess sound obstetric judgment and operative skill.

The dose should never exceed 3 minims (0.18 cc.) and is preferably 1 minim (0.06 cc.) Intervals between doses should be at least 30 minutes. This dose is not to be repeated if good contractions start

### Vaginal Antisepsis

According to Ziegler and Austin,<sup>11</sup> a sterile vagina in the adult female does not exist.

During the last 7 years vaginal antiseptis has been used as a matter of routine at the Elizabeth Steel Magee Hospital in about 17,000 cases of labor. It has been applied by means of the Kolpospray—an atomizer operated by compressed air with a pressure of about 35 pounds. The vagina is rapidly flooded and is thoroughly cleansed and flushed by the force of the spray. The secretions are mixed with the solution and blown out through the vents in the rear of the encasing tip as the escaping air under pressure returns unhindered to the atmosphere. The antiseptic used was a 1:2500 solution of tincture of merthiolate. Each patient is sprayed at the beginning of labor and every 8 hours thereafter until the completion of labor. Should the membranes rupture before labor begins, the spraying is done every 12 hours until labor begins. Vaginas are sprayed before each examination and before all operative procedures, including cesarean section, irrespective of when sprayed previously. When possible, an hour should elapse after spraying before operative procedures are un-

dertaken. A spraying should be timed to follow complete effacement of the cervix when possible. If an enema is to be given, it must precede preparation and spraying.

A comparison of 5140 cases, 2749 deliveries in 1932 before antisepsis was practiced and 2391 deliveries in 1937 (the fifth year of its routine employment) shows that of the first group 45.47 per cent were afebrile, 39.32 per cent had fevers from 99.2° to 100.2° F. (37.3° to 37.9° C.) and 15.21 per cent had fevers higher than 100.4° F. (38° C.). The respective figures for the 1937 group were 48.47, 42.37 and 9.16 per cent. The last percentage includes 287 unsprayed vaginas. In the 1932 group there were 8 deaths from peritonitis, 9 from septicemia, 5 from hemorrhage, 2 from pulmonary complications, 1 from a cardiac ailment, 7 from toxemia and 4 miscellaneous. The corresponding figures for the 1937 group were 3, 0, 4, 4, 2, 0 and 1. The authors state that vaginal antisepsis is an addition to and not a substitute for asepsis as practiced in every well conducted maternity.

## PLACENTA

### Placenta Accreta

Bosshardt<sup>12</sup> states that placenta accreta is being seen and recognized more frequently as the most serious complication of the third stage of labor. The condition results from a partial or complete absence of decidua basalis. Placenta accreta must never be confused with the rather common simple placenta retention seen in hourglass constriction or from some failure of the normal separating mechanism of a healthy placenta in a normal uterus. Since this condition can never be detected before delivery, it should be constantly kept in mind after the second stage of labor.

Treatment depends on prompt recognition. *Early hysterectomy* is the accepted treatment, preceded and followed by *blood transfusion*, if indicated, and the usual supportive agents for shock. Manual extraction of densely adherent placentas by hand, with placental forceps or by curet is extremely dangerous and predisposes to fatal hemorrhage or puncture of the uterus. In 11 cases treated by supravaginal hysterectomy with no attempts at extraction of the placenta there were no deaths. There were 6 deaths among 30 cases in which abdominal hysterectomy after partial manual extraction was employed. Manual extraction or curettage without hysterectomy for 31 cases resulted in 20 deaths. The combined mortality of the treated series reported in 1931 showing 86 cases with 32 deaths was 37.2 per cent. The author's cases bring the total to 101. His patient, even after procrastination for 9 days and adopting the hazardous method, unknowingly, of partial manual extraction, recovered after a subtotal hysterectomy.

### Placenta Circumvallata

Hobbs and Price<sup>13</sup> observed 150 cases of definite placenta circumvallata in 20,720 deliveries or 0.8 per cent.

Placenta circumvallata may be defined as an abnormal development of the placenta, characterized by a restricted growth of the chorionic plate, with oblique growth of its marginal villi into the surrounding decidua vera to form an extrachorial margin of placental tissue around part or all of its circumference. The membranes which insert into the edge of the plate become reduplicated and form a fold lying on the plate and constitute a wall of varying thickness around it.

If the fold is not present, the condition is commonly spoken of as placenta



marginata. The term placenta circumvallata is reserved for the type with the fold of membranes and is considered as only a further development of the secondary changes incident to the limit of growth of the chorionic plate

The fetus may be affected in the following ways: First, restriction of the growth of the plate and the inability of the villi to create new placenta spaces sufficient to meet all the increasing demands of the fetus, may lead to death. This placental deficiency may be augmented by placental infarction. If the fetus perishes early, abortion will occur. Later in pregnancy the placental reserve may be used up and the fetus may die just before term. Under ideal conditions the placental reserve may be sufficient to carry the fetus to term.

The usual effects on the mother are as follows: (1) Hemorrhage from incomplete abortion, although these abortions are usually complete, because they occur after the placenta has developed. (2) Blood loss from rupture of the marginal intervillous spaces as described above. It causes irregular, painless bleeding simulating placenta previa, especially if it occurs during the last trimester of pregnancy. (3) Occasional difficulty in the separation of the placenta because of the abnormal growth of the villi deeper into the decidua and occasionally into the uterine muscle.

A fetal mortality of 14 per cent in babies born after the twenty-seventh week emphasizes the seriousness of placenta circumvallata. A total mortality of 33 per cent places this abnormality as one of the outstanding feticides.

The authors call attention especially to the uterine bleeding produced by this condition. Thirty-three cases showed prelabor bleeding. It was painless, intermittent in character; although it lasted several weeks at a time, it was usually

mild. It occurred at any time during pregnancy and was not always followed by the onset of labor. Many patients bled intermittently for many weeks and delivered a live infant at term. In none of the patients was the bleeding serious, and with bed rest and sedation there was a tendency for cessation of bleeding. If the fetus perished, labor usually soon followed.

The most important clinical aspect of this condition is the awareness that painless bleeding during the last trimester is not always pathognomic of placenta previa. A few of these cases were brought into the hospital with that tentative diagnosis. Vaginal examination failed to confirm the diagnosis of placenta previa, and with bed rest the bleeding usually ceased. Unlike placenta previa, bleeding from a circumvallate placenta does not tend to be more severe with each recurrence. It is extremely important to be aware of this condition, for although there is little to be done for these patients, it is a serious mistake to treat them actively for the mistaken diagnosis of placenta previa. Twelve patients had retained placenta.

The incidence of syphilis (25 per cent of 107 known cases) was about twice the average in the clinic population. Many of these cases were under antisiphilitic treatment before the onset of pregnancy, and all syphilitic patients received treatment as soon as diagnosed, no matter what the stage of pregnancy. The etiologic relationship, if any, of syphilis to the formation of placenta circumvallata is not clear. Four cases of hydorrhea gravidarum associated with placenta circumvallata were noted.

### Placental Transmission of Sulfanilamide

Using rats in carefully controlled experiments, Speert<sup>14</sup> reports observa-

tions on the placental transmission of sulfanilamide. He found that administration of this drug to rats throughout gestation results in the appearance of sulfanilamide in approximately equal concentrations in the blood streams of both mother and fetus. Prolonged administration of sulfanilamide to pregnant rats produces deleterious effects in the offspring, including increased intra-uterine and postnatal mortality, decreased litter size, diminished birth weight and selective stunting of growth. It is concluded from these studies that until the effects of sulfanilamide on the human fetus are better known the drug should be administered with extreme caution during pregnancy. The necessary observations in human beings should include a careful study of intra-uterine development, birth weight and postnatal growth in the infants born to mothers receiving extended sulfanilamide therapy during pregnancy.

### Placental Visualization

Dippel and Brown<sup>15</sup> discuss direct visualization of the placenta by soft tissue roentgenography in examining 200 pregnant women. One-fourth of these patients were so studied because of bleeding in the last trimester. The placenta was visualized in approximately 90 per cent of the cases; in the others deterring factors were present which rendered visualization difficult or impossible. Such factors were hydramnios, multiple pregnancy, unusual obesity of the mother and prematurity. Although with immature fetuses the chances of visualization are definitely reduced, the authors demonstrated the placenta clearly in a pregnancy advanced to only the twenty-fourth week. The position of the fetus does not deter good visualization. When the placenta is implanted over the lower uterine segment,

its lower margin is usually not perceived. However, if one reasons that the normal placenta at or near term covers approximately one-fourth of the surface area of the uterine wall, the probable type of placenta previa may be diagnosed with reasonable accuracy.

In a few of the patients the location of the placental site was checked at cesarean section or by vaginal examination, and in no case was the x-ray diagnosis erroneous. The future course of the pregnancy in all cases conformed to the x-ray diagnosis. Since the adoption of this technic, the number of vaginal examinations has been greatly reduced. After being roentgenographed, many patients are discharged to carry on the pregnancy and to be delivered normally at or near term. A single lateral roentgenogram is usually sufficient.

Other applications of the technic offer possibilities. Before performing a cesarean section on a patient with an anteriorly located placenta, one might wish to take additional precautionary measures in the way of facilities for transfusion or to choose between a classic and a low cervical cesarean incision. Exact knowledge of the site of attachment before the insertion of bougies will guide one in selecting the anterior or posterior uterine wall for this and lessen the possibility of separation of the placenta. With the advent of soft tissue roentgenography the comparative thickness of the anterior uterine wall and the soundness of an old cesarean scar can be determined. To date the authors have seen 2 cases in which the anterior uterine wall appeared irregularly thinned, and the patients were not permitted to go through normal labor. This thinning was subsequently confirmed at operation.

**Visualization by X-ray Soft Tissue Technic**—Dippel and Brown<sup>16</sup> re-

port their results in 262 examinations for localization of the placenta by direct visualization.

The placenta was clearly visualized by soft tissue roentgenography in 236, or

factory x-ray films were obtained in 3.05 per cent of the cases, and it was impossible to visualize the placenta in 2 of 8 cases of twin pregnancy. Immaturity, provided the pregnancy has advanced



Fig. 11—Roentgenogram of a multipara near term, who went into labor following premature spontaneous rupture of the membranes. Rectal examination upon admission to the delivery ward precipitated moderate vaginal bleeding. The placenta was visualized over the anterior wall of the lower uterine segment with its thickest region located by the lower arrow. The upper arrow is directed toward the anterior wall of the fundus, which is of normal thickness. The lumbar region of the fetal spine and the buttocks are flush against the placenta. This location of the placenta (placenta previa) was confirmed at the time of delivery by low cervical cesarean section. (Dippel and Brown: *Am. J. Obst. and Gynec.*)

90 per cent, of 262 observations on 259 patients, in 261 pregnancies. The greatest factor interfering with visualization was found to be hydramnios, and accounted for nonvisualization in 5.73 per cent of the roentgenograms. Unsatis-

beyond the midpoint, and abnormal presentations and positions are not hindering factors in visualization.

Calcification of the placenta is rarely extensive enough to aid in localization of the placental site. No other adjuncts

to actual visualization were found. Fetal position is not a reliable criterion of the location of the placenta.

No errors in roentgenologic localization of the placenta were found in the 53 instances which were checked by reliable clinical methods.

The placental implantations were almost equally divided between anterior and posterior walls of the fundus. However, with low implantation, essentially 8 times as many placentas were found implanted on the anterior as on the posterior wall of the lower uterine segment.

The average thickness of the walls of the fundus uteri near term measured 1.24 cm. on the roentgenograms which were made at a distance of 42 inches.

Only 11 (12 per cent) of 92 cases of vaginal bleeding were found roentgenographically and clinically to have true placenta previa; 15 other cases presented merely x-ray evidence of low implantation of the placenta, without the usual clinical signs.

Soft tissue roentgenography in obstetrics finds its greatest usefulness in those cases of vaginal bleeding where the whole of the placenta can be visualized above the level of the iliac crests and these constitute the great majority, 88 per cent, of the instances of vaginal bleeding in the latter months of pregnancy.

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## PREGNANCY

### Complications of Pregnancy

**Abdominal Pregnancy**—From his own experience in observing 5 cases of abdominal pregnancy Lull<sup>17</sup> discusses the management of this rather rare condition. The advisability of delaying operation with the idea of obtaining a living child is questionable, inasmuch as many of these children have congenital abnormalities and the risk to the mother

in deferring operation seems to be greatly increased. When the diagnosis is made late in pregnancy, waiting a week or two seems advisable but operation should be performed between the thirty-sixth and the thirty-eighth weeks. Permitting the patient to advance to full term increases the maternal risk and decreases the chances of having a living offspring.

If death of the fetus occurs, it seems advisable to defer operation for 3 or 4 weeks until the vascularity of the placenta has been markedly decreased and a partial separation has taken place. During the waiting period the patient should be kept in the hospital under close observation for hemorrhage and infection of the gestational sac. If the fetus has been known to be dead for several weeks, immediate operation is indicated.

Careful preparation for combating possible hemorrhage should be made before operation is attempted. The patient's blood should be typed and the necessary blood at hand, so that, if necessary, it can be given immediately.

Incision of the abdominal wall should be made over the site of the child rather than over the placenta. This of course is not always possible.

Careful removal of the child without disturbing the placental site is important. This is not always possible, however. When it is seen that the placenta will be partially detached in removing the fetus, the larger vessels should be ligated before attempt at separation is made.

When operating upon a patient where the fetus has been known to be dead for some time, the fact that removal of the placenta may still give rise to serious hemorrhage must not be lost sight of, and although removal can usually be accomplished, it is necessary in some

instances to resort to packing to control the bleeding. It seems advisable not to disturb the packing for at least 10 days.

In operating upon a patient where the fetus has been dead for some time and there is evidence of infection, approach to the sac should be made with care and if possible, extraperitoneally. These cases should always be drained and removal of the sac should never be attempted.

When hemorrhage is encountered and packing is necessary, removal of this packing, after it has been loosened on several successive days, should be attempted only after careful preparation has been made for further transfusion and reopening of the abdomen.

Where the placenta is alive and a living child removed, no attempt at separation or removal of the placenta should be made. The abdomen should be closed without drainage. The author points out, however, that the placenta does not always resorb and may even result in abscess formation. When the former occurs, removal of the placenta should be deferred for 2 months, unless there is evidence of abscess formation or intestinal obstruction, at which time immediate operation is indicated. If secondary removal becomes necessary and the entire sac wall cannot be removed, marsupialization with packing of the cavity seems to be indicated.

**Diabetes**—The prevention of accidents in pregnancy complicated by diabetes is reported by White and Hunt.<sup>18</sup> The authors noted from a study of 61 diabetic pregnancies that adequate dietary control of diabetes and insulin therapy did not lower the fetal mortality rate. They believe (1) that an abnormal rise of chorionic gonadotropin after the twentieth week to a level of 200 rat units per 100 cc. of blood in the diabetic predicts premature delivery, still-

birth and neonatal deaths, (2) that these accidents are caused by a failure of production or of metabolism of estrogen and progesterone and (3) that they are prevented by continuous substitutional *estrogen* and *progesterone therapy* in replacement doses.

The 61 patients studied fell into 3 groups, 25 whose hormonal balance was normal, 12 whose hormonal balance was abnormal and uncorrected, and 24 whose balance was abnormal but who received substitutional estrogen and progesterone therapy.

The clinical course and outcome of the 25 normal hormonal diabetic pregnancies was uneventful. None developed preeclamptic toxemia, none had premature deliveries, and fetal survival was 92 per cent. Of the 12 patients whose values were abnormal and who received no therapy, 9 developed preeclamptic toxemia, the remaining 3 had premature deliveries, and fetal survival was only 42 per cent.

Substitutional estrogen and progesterone therapy in replacement doses was therefore started. Thirteen patients were given daily doses of from 150,000 to 450,000 international units of *estradiol* and from  $\frac{1}{6}$  to  $\frac{2}{3}$  grain (10 to 40 mg.) of *benzoate proluton*. Toxemia was controlled, premature deliveries did not occur, and fetal survival was 92 per cent. Eleven patients were treated with oral *stilbestrol* in doses of  $\frac{2}{3}$  to 2 grains (40 to 120 mg.) daily.

The clinical results were comparable: Toxemias were controlled; no markedly premature deliveries occurred and, barring 1 case of fatal erythroblastosis, the third erythroblastic infant of this mother, the fetal survival was excellent, 90 per cent.

The present plan of treatment is oral therapy, but if the gonad stimulating factor called "prolan" is not falling to

satisfactory levels after 2 weeks' adequate trial with stilbestrol in doses up to 2 grains (120 mg.) daily, stilbestrol given intramuscularly up to  $\frac{5}{8}$  grain (50 mg.) is substituted for the oral preparation. Among 16 patients who have been or are being treated with massive doses of stilbestrol, no side reactions have occurred and no toxicity measured by bilirubin excretion tests has been observed.

The treatment of diabetes is the simplest part of the problem. The *diet* must be adequate, carbohydrate liberal, from 150 to 250 Gm., protein 2 Gm. per kilogram of body weight, fat to complete the caloric prescription of 30 calories per kilogram. *Medicinal minerals* and *vitamins* are added. *Insulin* dosage, to avoid the pitfalls of low renal threshold, is controlled by blood rather than urinary sugars.

**Ectopic Pregnancy** — Thirty-two cases of ectopic pregnancy with complete clinical and laboratory findings were analyzed by Goldblatt and Schwartz<sup>19</sup> with regard to the findings on curettage, the result of the Friedman test, the microscopic examination of the removed tube, and the clinical picture.

In a well-regulated hospital, a suspected case of ectopic pregnancy without acute symptoms may be observed with comparative safety for rather prolonged periods of time until the diagnosis is made. Seventeen patients were observed from 1 to 2 weeks and 4 patients still longer, without serious sequelae.

Any patient with an ectopic pregnancy who bleeds scantily, even for many weeks, may still have uterine decidua, but with a decreased decidual expectancy as the duration of the bleeding increases. If the bleeding has been moderate or profuse for more than 3

weeks, decidua is extremely likely to be absent.

No patient with a negative Friedman test had uterine decidua at the time of curettage. No patient with uterine decidua had a negative Friedman test. The authors also observed a close but not perfect relationship between the result of the Friedman test and the state of preservation of the chorionic villi. Occasionally they found morphologically perfect placental tissue in the fallopian tube, a positive Friedman test, and an absence of decidua in the uterus. Such patients always had a history of prolonged or profuse bleeding per vaginam.

Factors other than placental degeneration are probably important in causing decidual degeneration and expulsion. Among such factors may be the suddenness of placental degeneration, and the sensitivity and irritability of the decidua or myometrium.

If while under observation for several days or longer the patient's course has been febrile, the uterus appears less likely to contain decidua than if the temperature had remained normal.

In cases of suspected old ectopic pregnancy where the Friedman test is negative, aspiration of the cul-de-sac may confirm the diagnosis. Here curettage would reveal no decidua, but may nevertheless be indicated to rule out the presence of an old incomplete abortion or placental polyp.

**Leukorrhea** — Liston and Cruickshank<sup>20</sup> found the vaginal discharge to be normal in only 40 of 200 pregnant women supposed to be suffering from leukorrhea. By normal the authors mean that pus cells were less numerous than epithelial cells, the bacterial flora consisted wholly of Döderlein's bacilli, the pH of the vaginal contents lay between 4 and 5, and glycogen was abundant in the epithelial cells.

Cervical lesions, including erosions, were present in 79 of the 200 cases. More than half of these cases were complicated by other causes of leukorrhea. The condition of the cervix of 31 women was the possible explanation of the leukorrhea. The more severe forms of cervical lesions were associated with abnormal features of the vaginal contents, for pus cells became more numerous, the bacterial flora tended to drift toward types 2 and 3, the hydrogen ion value was less acid, and glycogen was less abundant in the epithelial cells. There were only 4 cases of gonorrhea. The parasite of vaginal thrush was the cause of the leukorrhea in 49. This infection is easily overlooked unless films are made from the white patches characteristic of the disease. The diagnosis should be made by finding the hyphal filaments of the fungus. The blastospores of this fungus may be confused with yeast cells.

*Trichomonas vaginalis* was responsible for the leukorrhea of 75 of the 200 women. In all these cases pus cells predominated over epithelial cells in the vaginal films, and the majority of the cases presented a bacterial flora of type 3. The  $pH$  of the vaginal contents lay generally between 5 and 6. Recovery was associated with a return of the  $pH$  to between 4 and 5, and this was associated with a change in the type of the bacterial flora from type 3 to 1 through type 2. Glycogen was generally deficient in the epithelial cells. The condition was in some cases complicated by cervicitis, thrush or gonorrhea. Eight of the 200 cases could not be classified. Some of these patients showed a thin, watery discharge with numerous epithelial cells, comparatively few pus cells, large numbers of organisms of type 3 and  $pH$  about 6. No cause for this type of leukorrhea was apparent.

**Pyelitis**—The management of pyelitis based on 117 cases among 5960 deliveries at the Mayo Clinic is discussed by Mussey and Lovelady.<sup>21</sup> Seventy-two of the patients were primigravidas and 45 multigravidas, bearing out some previous reports that pyelitis occurs more frequently among the former. There were 92 instances of ante-partum and 25 of post-partum pyelitis. Post-partum pyelitis was usually of mild degree and did not exhibit the usual symptoms of pyelitis of pregnancy. Previous infection of the upper part of the urinary tract plays a part in the recurrence of pyelitis in subsequent pregnancies; however, only 12 of the present patients gave a history of pyelitis prior to the first pregnancy and none gave a history of urinary infection in childhood. The data of the 117 cases do not confirm the assertion that pyelitis increases the hazard of pregnancy. There were 4 spontaneous abortions and 2 premature labors.

Labor was induced because of pyelitis in 7 cases but not before viability. One of 117 patients died. Acute pyelitis was rarely the cause of preeclamptic toxemia or eclampsia among the series discussed. Although pyelitis is not a common complication of pregnancy it occurs with sufficient frequency to necessitate alert diagnosis and treatment before permanent renal damage occurs. Whenever pus is found in a specimen of urine during periodic ante-partum examination a specimen of urine obtained by catheterization should be examined for pus, for pyelitis without subjective symptoms may be present.

The 121 patients have been divided into 4 groups. Group 1 received *large quantities of fluids* and usually one of the *urinary antiseptics*; group 2 was treated by *ureteral catheter drainage*; group 3 was given one of the various

*mandelic acid* preparations; and group 4 includes the 4 patients given *sulfanilamide*. The results of administering large quantities of fluid to 64 patients were uniformly good and indicate that in more than one-half of the cases pyelitis of pregnancy will respond favorably to forced fluids and rest in bed. These measures were most effective when applied early in the course of the disease. In group 2, 48 patients, there were acutely ill patients who failed to respond to the treatment outlined in group 1, and indwelling catheters were inserted for adequate drainage of the renal pelvis.

From 1924 to 1933 ureteral drainage was used in approximately 57 per cent of patients with proved pyelitis of pregnancy. Since 1933 this treatment has been employed in approximately 19 per cent of the cases. When pyelitis of pregnancy is recognized and treated in its early stages, a majority of patients will recover following a regimen of *rest in bed, sedatives and forced fluids*. The effect of this management has been a continuing decrease in the number of patients requiring ureteral catheterization. Since the advent of chemotherapy, this will no doubt become still less. The only death of the entire series occurred in this group. *Mandelic acid* was used for the 5 cases of group 3, and the response to treatment was uniformly good. The response of the 4 patients in group 4 to sulfanilamide was good. Further observation may indicate the advisability of employing *azosulfamide* or other allied products.

The methods of avoiding and minimizing *pyelo-ureteritis gravidarum* are described by Traut, Bayer and McLane.<sup>22</sup>

At each antepartum visit, the normal obstetric patient should be questioned concerning dysuria, frequency and pain

in the kidney region. Should any of these be experienced, a sterile catheter specimen of bladder urine should be obtained and scrutinized microscopically. Should clumped white blood cells be seen, the remainder of the sterile specimen should be sent to the bacteriologic laboratory for culture. In the meantime, *fluids are forced* and the patient is given 60 grains (4 Gm.) of *sodium bicarbonate* after each meal.

Not infrequently the first indication of urinary tract infection is a cloudy precipitate produced in the urine by the test for albuminuria. When this is seen, in the absence of any supportive evidence for the diagnosis of toxemia, a sterile catheterized specimen of bladder urine should be taken and cultured for *B. coli*, whether any white blood cells are seen in the microscopic specimen or not.

As soon as the positive report of bacteriologic culture for *B. coli* is obtained the patient is placed on an ambulatory *sulfanilamide* treatment. The patient is provided with 25 5-grain (0.3 Gm.) tablets of sulfanilamide and is instructed to take 1 tablet on awakening, 1 after each meal and a fifth on retiring. With each of the postprandial pills the patient is instructed to take a teaspoonful of sodium bicarbonate dissolved in water. Fluids are limited to the lowest amount consistent with comfort (about 1500 cc. daily). The treatment is valuable in controlling the early stages of the infection. The course is repeated after 1 week's rest until a series of 3 negative urine cultures are obtained. Thereafter the urine is cultured once a month until delivery. Should a positive culture again be obtained, the ambulatory sulfanilamide therapy is repeated.

The patient who offers a history of previous infection of the urinary tract is



treated quite differently in that she is given less leeway because of the greatly increased chance of the development of infection during pregnancy.

Whether the acute attack occurs as a primary entity or as a recrudescence of long-standing disease, certain elements of therapy are fundamental. The first is hospitalization. Bladder cultures are repeated together with microscopic examination of the urine, to determine the type and severity of the inflammatory reaction. The blood nonprotein nitrogen level is determined every second or third day to rule out nitrogenous retention due to cortical damage. Intravenous pyelograms are taken to throw the kidney pelvis and ureters into view and also to give information as to kidney function. In addition, these patients are given large doses of sulfanilamide commencing with from  $1\frac{1}{2}$  to 2 drams (6 to 8 Gm.) a day in divided dosages, with limited fluid intake the first 2 days, and thereafter a dose of the drug sufficient to maintain a concentration in the blood of from 8 to 10 mg. per 100 cc. and concentration in urine above 100 mg. per 100 cc. With the great majority of patients the temperature returns to normal after a few days of this treatment, and after 3 or 4 days of normal temperature the patient is discharged to be followed in the antepartum clinic. The incidence of the disease has been reduced 50 per cent with this régime.

Post-partum pyelitis has been almost completely eliminated by the use of small doses of sulfanilamide and sodium bicarbonate administered prophylactically to all patients having infected bladder urine with symptomatic cystitis. In addition, pyelonephritis has come to be almost nonexistent because the authors do not allow the disease to progress to the point where this complication is possible.

## Toxemias of Pregnancy

**Pernicious Vomiting** — The treatment of 225 consecutive cases of pernicious vomiting encountered among 39,724 pregnant women in the Boston Lying-In Hospital for the past 12 years is discussed by Irving.<sup>23</sup>

Only 73 were patients registered for care in the clinic; the remainder were sent in as emergency cases and were generally from a higher economic stratum than those usually accepted at the clinic. Contrary to the usual opinion, 61.3 per cent of the patients had been pregnant before. Of the 138 multigravidae affected, 70 had vomited excessively in 1 or more previous pregnancies. The greatest number entered between the sixth and twelfth weeks of gestation. The patients with pernicious vomiting showed later in pregnancy no more tendency toward preeclampsia than did the others in the clinic; the ratio in their case was 1:22.5, and the general ratio 1:21. All pathologic reports show the hepatic change to be the same fatty degeneration that follows extreme starvation. The necrotic changes reported by earlier writers were not seen. A pulse rate of 110 or more always indicates a very sick patient.

Peripheral neuritis is the most serious complication. Other complications are puerperal psychosis, pyelitis, pulmonary tuberculosis, hydatidiform mole, renal tuberculosis and acute appendicitis.

For the mildly affected patients not requiring hospitalization, **reassurance**, a **fat free diet** rich in carbohydrates taken in small amounts 6 or 7 times a day and a **mild sedative** usually suffices. For the seriously sick patient, hospital care under **complete isolation** from friends and family, including the husband, is necessary. The lower part of the intestine is emptied by enemas, and

from 3 to 9 grains (0.2 to 0.6 Gm.) of *pentobarbital sodium* or any suitable barbiturate is given by rectum and repeated often enough to maintain the patient in a somnolent condition. Opiates are avoided, as they appear to increase vomiting. A *hypodermoclysis* of 1500 cc. of physiologic solution of sodium chloride is then given and sufficient daily amounts are administered to maintain fluid balance. An intravenous drip of 5 or 10 per cent *dextrose* is given at 30 to 40 drops a minute and repeated at from 8 to 12 hours.

From January, 1928, to January, 1934, 110 patients were treated in this manner; 6 died and 19 were subjected to therapeutic abortion. As the pathologic changes of the patients who died were those of starvation, the Levine nasal tube as a method of forced feeding was used and improvement was at once apparent. Up to January, 1940, 115 patients were treated in this way with no deaths and only 3 therapeutic abortions. At present, in addition to the described regimen, the Levine tube is passed and the stomach gently washed with warm water. A half hour later a rectal drip is started. From 4 to 6 ounces (120 to 180 Gm.) of milk containing 2 heaping teaspoonfuls of Harris yeast concentrate is given by the Levine tube, followed in an hour by 4 to 6 ounces of orange juice sweetened with Karo corn syrup and 1 hour later by 6 ounces of a rich eggnogg made with cream and egg, and 1 hour later by milk and the Harris yeast concentrate. This routine is repeated until 14 out of 25 hours are completed. Each feeding requires about 40 minutes and is given at body temperature.

*Thiamin hydrochloride*, *ascorbic acid* and *liver extract* are given intramuscularly. If in spite of these measures there is a steadily rising pulse which

remains above 110 or if the vomiting with jaundice is intractable the *pregnancy* should be *interrupted*. If 24 hours may be devoted to the process, the safest procedure is to *pack the cervix and vagina firmly* and the next day, after sufficient dilatation, to *remove the ovum* with a placental forceps and a dull curette. If such time cannot be taken, *vaginal hysterotomy* may be performed.

*Preeclampsia* — So-called preeclampsia is characterized (1) by an inordinate gain of body weight throughout pregnancy—in the early months as latent water retention, in the last trimester as frank edema; (2) by low or normal blood pressure in the early months followed by rather sudden climbing blood pressure in the last trimester; (3) by normal urinary findings in the early months, followed by frank albuminuria in the latter months of gestation. This group of signs may eventuate in anuria and convulsions at the time of reaching their peak, or they may, on the other hand, be sharply interrupted by a termination of the pregnancy, spontaneous or induced, whereupon there is characteristically a voluminous diuresis, gradual reduction in blood pressure, and a clearing of the albuminuria.

Anderson<sup>24</sup> has observed that frequently there is a history of previous food preference along the line of carbohydrates rather than proteins, such as meat, fish, eggs, and milk. He states that a pregnant female, using a diet of 50 Gm. or less of protein, will be far more susceptible to water retention and edema.

The author points out the empiricism of colonic irrigation with bicarbonate of soda, of sweating the patient to make up for a supposedly deficient renal function, of imposing on her the burden of caloric or protein starvation, is of the past.

The cause of waterlogging in the eclamptic syndrome is not known; nevertheless, methods of treatment which encourage water retention should logically be avoided. First of all, sodium, whether this be in the form of sodium chloride, sodium bicarbonate, or sodium bromide, should be scrupulously reduced to a minimum, since its accumulation in the intracellular tissue spaces makes for water affinity. It is wrong to have patients placed on a salt-low diet of 2 to 3 Gm. daily and at the same time given sodium bromide by rectum at the rate of 1 to 1½ drams (4 to 6 Gm.) a night for sedation. *Ammonium chloride* and *calcium chloride* are useful for their acidifying effects in order to produce diuresis and a mobilization of sodium from the tissue spaces. The old vogue of alkalinizing the eclamptic patient by drug or diet is born of ignorance.

The protein content of 1½ quarts of milk approximates 50 Gm., making up, somewhat, for the protein starvation. The free use of carbohydrates is also recommended as a normal human being will always, if it is available, metabolize carbohydrate in preference to, and more efficiently than, protein and fat. Carbohydrate is also an effective agent available to protect the liver.

The author advises, therefore, a *diet* of 1.5 to 2.0 Gm. of protein per kilo, or for the 132-pound female, 90 to 120 Gm. Since much of the protein in the average diet is plantborne, and therefore certainly less efficient, it is probable that an arbitrary figure of 150 Gm. of protein is more satisfactory, of which 110 Gm. should be as animal protein. The carbohydrate of the diet should be close to normal, namely, 300 to 350 Gm. Fat should be low, from 55 to 60 Gm. The diet should be low in sodium chloride (2 Gm. daily or less), high in calcium and potas-

sium by virtue of a liberal milk allowance, and should meet Sherman's optima for vitamins. Vitamin D and the vitamin B complex will be of advantage when added. Such a diet will range between 2295 and 2540 calories.

The estrogen and progestin metabolism in pregnant women with preeclampsia has been the subject of investigation of Smith and Smith.<sup>25</sup> A rise in the gonadotropic potency of the serum after the fifth month of pregnancy is followed by a decreasing production of progestin and of estrogen. Such a phenomenon may reflect a decreasing utilization of the pregnancy gonadotropic factor for the elaboration of estrogen and progestin. The deficiency of these 2 steroids results in a deranged metabolism of both, involving less complete conversion and utilization and more rapid destruction. Such a shift in steroid metabolism pertains at the onset of normal labor. When this change occurs prior to term, it is accompanied by the clinical signs of preeclampsia (or by premature delivery).

Because of the more rapid destruction which accompanies the mutual deficiency of *progestin* and *estrogen*, and because of the fact that each of them, in adequate amounts, is required for the proper metabolism of the other, a re-establishment of a normal hormonal balance by replacement therapy can only be accomplished by the continued injection of both of them in large amounts. There is evidence that clinical improvement accompanies the establishment of a normal balance.

Testosterone propionate has an effect similar to that of progestin upon the metabolism of the estrogens. It also appears to protect both estrogen and progestin in preeclampsia, however, because its prolonged administration apparently suppresses the elaboration of progestin (and possibly estrogen) and

may have other undesirable effects due to its androgenic nature.

The administration of progestin and estrogen as a therapeutic measure in preeclampsia is as yet of very limited clinical value for 3 reasons: (1) the large amounts required are not commercially available in sufficiently concentrated form and are still too costly; (2) in the amounts and kind administered in this study, injections must be continued for at least 6 days before any effect upon the hormonal or clinical picture can be expected. In fulminating preeclampsia such a delay is not justifiable; (3) The indications are that in cases of greater severity than any herein reported, in which estrogen and progestin destruction may be even more rapid, replacement therapy would be of no avail.

*Treatment with Estrogen*—The protocols of 7 more pre-eclamptic and 2 convulsive eclamptic patients treated with *estrogens* in huge doses are reported by Shute and Barrie.<sup>26</sup> These women were not restricted as regards activity or diet except for limitation of sodium chloride in several of them.

Barrie, working in England, has recorded eclamptic-like convulsions in certain E-defective rats suddenly given large doses of d-1-a tocopherol. The histologic lesions in these animals simulated those of human eclampsia. This theory that estrogen defect is an important factor in the onset of eclampsia is related as vitamin E is antiestrogenic in character.

The clinical effects of estrogens on these women are slow in developing, but favorable influences on convulsions, stupor, blood-pressure, urinary volume, and albumin have been observed by these authors.

**Remote Effects of Toxemia of Pregnancy** — Lewish<sup>27</sup> offers an instructive follow-up of cases of toxemia

of pregnancy. The author followed for from 1 to 12 years 70 cases of nonconvulsive and 37 cases of convulsive toxemia in subsequent gestations. Of the 70 cases in the nonconvulsive series recurrent toxemia developed in 43, 18 showed no ill effects following the toxemia and permanent vascular renal diseases developed in 4.

The duration and severity of the toxemia before the birth of the child seems to be an important factor in the development of permanent vascular renal disease. The age, parity and the degree of hypertension may be of equal importance. However, these factors play a minor part in the convulsive group. Recurrent toxemia may appear in the absence of any detectable sign of renal impairment. The prognosis seems to be more favorable in the convulsive group if the patient survives the initial toxemia.

If all patients who have had late toxemia of pregnancy would report for antepartum care as soon as pregnancy is suspected, the incidence of eclampsia would be greatly reduced and the mild forms of toxemia would be discovered and dealt with earlier. A precise knowledge of the time and mode of onset of a toxemia would be helpful in evaluating the danger of continuing the pregnancy. In this way cardiovascular renal disease would not develop in many women at an early age and it would probably be postponed for many years. Antepartum care is imperative if the major risks are to be avoided, especially as the rapid recovery which usually follows 1 attack gives the patient a false sense of security. The author believes that no woman should be exposed to further risk if she has had 2 or more toxic pregnancies.

### Fetal Endocrines

The problem of the function of the fetal thyroid during pregnancy is

presented by Zondek.<sup>28</sup> A patient with idiopathic myxedema became pregnant after 2 years' treatment with thyroxin and gave birth to a normal child. During the first 3 months of pregnancy, symptoms did not appear; only the heart showed slight dilatation of the left ventricle, flattening of the PT deflection and lowering of the RS complex as the first indications of a beginning relapse. These changes became apparent during treatment with thyroxin and suggested that the pregnancy had an injurious effect on the maternal thyroid gland. At this point treatment with thyroxin was discontinued but, contrary to expectation, further symptoms did not appear up to the period after delivery. In the ninth month the basal metabolic rate was —1 per cent as compared with —29 per cent before the pregnancy and before the patient was given thyroxin.

Shortly after delivery all the typical symptoms reappeared with "dramatic rapidity"—marked puffiness of the face, swelling of the eyelids, hands and feet, low and rough voice. Six weeks after delivery the basal metabolic rate was —29 per cent and the heart showed the typical alterations observed in myxedema. Thyroxin treatment once more effected improvement of all these symptoms. Zondek concludes that the sudden relapse after termination of pregnancy must be connected with the fact that the substituted activity of the fetal thyroid which had existed during the last months of pregnancy was no longer present.

### Fetal Weight Control

L. E. Arnold<sup>29</sup> reports an attempt to control fetal weight by administration of thyroid during pregnancy. Clinical investigation has proved that maternal weight can usually be controlled by dietary restrictions; however, these restrictions have no effect upon fetal weight.

Realizing that maternal dietary excesses do not cause fetal obesity, the most reasonable etiologic factor is a disturbance in thyroid metabolism.

A series of 116 patients was started, based upon the thesis that fetal obesity is due to a fetal thyroid deficiency which can be corrected by placing a sufficient saturation of *thyroid extract* in the fetal blood strain. These women were given thyroid extract orally during 4 or more months of their pregnancies. Each patient received not less than 3 grains (0.2 Gm.) and not more than 6 grains (0.4 Gm.) daily. Armour's enteric coated 1-grain (0.065 Gm.) tablets were used on all cases. These patients received no other medication that could influence weight and they were told to eat a normal, well-balanced diet without qualitative or quantitative food restriction. They were given no extradietary calcium or vitamins.

These women were seen at intervals of not less than 2 weeks, at which time routine prenatal care was given; in addition, they were carefully examined for evidence of hyperthyroidism. The fact that these signs failed to develop in a single case is significant and further proves clinically that there is a thyroid deficiency during pregnancy.

The average maternal weight gain during entire pregnancy in this group of 116 cases was 18.2 pounds (83 kilograms). The average fetal birth weight was 6.8 pounds (3090 Gm.). There was no fetal mortality or prematurity and no maternal mortality. No baby weighed more than 7 pounds 12 ounces (3522 Gm.) and none less than 5 pounds 11 ounces (2590 Gm.).

### Intrauterine Death

Intrauterine death of the fetus after the twenty-eighth week offers a most

interesting field for investigation. Buxbaum and Udesky<sup>30</sup> attack the problem not from an etiologic standpoint but as to the management of these cases.

Intrauterine death of the fetus in the clinic of the Chicago Maternity Center occurred 128 times in 16,834 deliveries, an incidence of 0.7 per cent. This complication occurred more frequently in women over 30 years of age.

Seventy per cent of the patients went into labor spontaneously within 7 days after the known death of the fetus. The remaining 30 per cent did not go into labor for a period varying from 7 to 56 days. There was a marked tendency for this complication to occur in patients having a previous history of repeated abortions or stillbirths.

Despite the fact that fewer deliveries occurred in the para V to para X group, this group still accounted for 50 per cent of the total number of fetal deaths in this series, indicating an increased tendency for intrauterine death of the fetus to occur in the higher parities.

The commonest causes for death of the fetus during pregnancy where such causes could be ascertained, were syphilis, late toxemias of pregnancy including chronic nephritis and diabetes.

Spontaneous onset of labor occurred in 92.1 per cent, and in 7.9 per cent labor was induced because of maternal complications. Delivery occurred spontaneously in 86.8 per cent, and was terminated by operative means in 13.2 per cent. However, 13 of these operative cases were craniotomies, most of which were done for teaching purposes.

One hundred sixteen, or 90.7 per cent, of these patients had a normal uneventful convalescence. There were no maternal deaths in this series. The authors conclude that intrauterine death of the fetus, regardless of the period of reten-

tion in the uterus, produces no serious untoward effects on the mother, and if managed conservatively should be attended by no maternal mortality.

### Maternal Mortality

E. F. Daily, Director of the Division of Maternal and Child Health, U. S. Children's Bureau,<sup>31</sup> calls attention to the fact that the application of the best existing knowledge of maternal care to an increasing number of women is being rewarded by an extremely significant decrease in maternal deaths. The lowest mortality rate ever recorded in the United States, 43.5 per 10,000 live births, has been reported by the United States Bureau of the Census for the year 1938. For the first time on record less than 10,000 (9953) deaths were assigned to puerperal causes. The number of live births registered in 1938 was 2,286,962, a birth rate of 17.6 per thousand of population. This was a slight increase over 1937.

The maternal death rate for all causes decreased 11 per cent during the year 1938 (from 49 per 10,000 in 1937 to 43.5 per 10,000 in 1938). The combined rate for abortion and ectopic pregnancy decreased 16 per cent; the rate for puerperal sepsis, including phlegmasia alba dolens, and so on, decreased 12 per cent; the rate for all toxemias decreased 11 per cent, and the combined rate for puerperal hemorrhage and other accidents of childbirth decreased 7 per cent.

Deaths from abortion and ectopic gestation in 1938 have been grouped together because they represent largely deaths occurring early in pregnancy. Deaths from accidents of pregnancy have been combined with those caused by puerperal hemorrhage because they are largely due to hemorrhage and shock associated with delivery. Deaths from phlegmasia alba dolens and other

causes in this group are combined with those caused by puerperal septicemia because they are the result of infection. All toxemias are grouped together because it is impossible to separate satisfactorily each type of toxemia on the basis of information on death certificates. These are largely deaths from eclampsia, preeclampsia and nephritic toxemia (not including chronic nephritis, which is considered nonpuerperal). Deaths from accidents of pregnancy include deaths of undelivered women. These have been combined with the small number of deaths unclassified as to cause.

Approximately one-fourth, 23 per cent, of the maternal deaths resulted from abortion or ectopic gestation, while three-fourths are concerned with complications of late pregnancy, delivery or the puerperium, 27 per cent due to puerperal hemorrhage and other accidents of labor; 24 per cent due to puerperal septicemia and 25 per cent due to toxemias of pregnancy.

From 1930 through 1934 the maternal mortality rate decreased only 12 per cent. From 1934 through 1938 the maternal mortality rate has decreased 25 per cent.

The decline of 14 per cent in 1937 as compared with 1936 and 11 per cent in 1938 as compared with 1937 represents a decrease of 23 per cent of the maternal mortality rate in the United States in the 2-year period 1937 through 1938. There would have been 5370 more maternal deaths in 1938 if the maternal mortality rate of 1930 had applied in 1938.

### Retrodisplacement of the Uterus

The relationship of retroversion and its associated conditions to pregnancy is discussed by A. H. Aldridge.<sup>32</sup>

Retrodisplacements are not infrequently the cause of sterility, early abortion, and unpleasant symptoms following abortion and delivery. Unless it is known that retroversion preceded pregnancy, postabortal and post-partum retroversion should be treated by palliative means to reduce the incidence of permanent retrodisplacements of the uterus. Selection of cases for treatment by surgical means should be based on painstaking physical examinations and therapeutic tests to be sure that preoperative pelvic symptoms are gynecologic in origin. Associated functional and pathologic conditions of the uterine adnexa more frequently constitute indications for operation than retrodisplacement of the uterus.

Operations for the cure of retroversion and its associated conditions should usually be aimed at preserving the child-bearing function and establishing anatomic and physiologic conditions which will be favorable for subsequent pregnancies. Since retroversion of the uterus is caused by relaxation of the broad as well as the round ligaments, the author claims that operations should be done by technics which restore the function of the broad as well as the round ligaments. He favors the *Bissell operation*.

The incidence of failure in operations for retroversion could probably be reduced if conception could be postponed until at least 6 months after operation.

### Pregnancy Test

A study of *false Friedman tests* for pregnancy was made by L. M. Randall, T. B. Magath, and F. N. Pansch.<sup>33</sup> The Friedman test is based on quantitative considerations. Excretion of the gonadotropic principle of the anterior lobe of the hypophysis in the urine in excess amounts may be responsible for a

positive Friedman reaction in the absence of pregnancy.

Among the several physiologic and pathologic states other than normal pregnancy which may give a positive reaction are hydatidiform mole, chorioepithelioma, the menopause, menstrual disorders such as primary ovarian failure, treatment with preparations of the anterior lobe of the pituitary gland and errors in technic.

A negative reaction to the Friedman test prior to the seventh week after the last menstrual period may not be conclusive, although authentic positive reactions may be obtained much earlier, frequently within 4 weeks after impregnation. A test that gives negative results before the seventh week should be repeated later.

E. P. McCullagh and W. K. Cuyler,<sup>34</sup> obtained 241 false positive reactions in 2134 cases. Of 1774 tests in women 172 yielded positive reactions, and of 360 tests in men, 69 yielded positive reactions. The authors emphasize that in considering the positive reactions in these cases it should be remembered that all tests were done on persons suspected not of pregnancy but of some endocrine abnormality, and the frequency of positive results is thus not comparable to the so-called false positives found in cases in which the test was done for suspected pregnancy.

For purposes of analysis the authors divide cases showing *positive Friedman* reactions into several groups: Conditions associated with disorders peculiar to women; conditions associated with or due to testicular deficiency or tumor, endocrine disorders that are not sex specific, disorders of the nervous system and of the pituitary and conditions not clearly endocrine in nature. They emphasize that the test is frequently positive about the time of puberty, possibly

for physiologic reasons. It may be positive in psychoses, hysteria, epilepsy and arterial hypertension in the absence of gonadal failure and may be useful in the differential diagnosis of pituitary cachexia and anorexia nervosa. Primary disease of the pituitary such as acromegaly or pituitary tumor and also organic lesions in the hypothalamus may cause positive reactions. In cases of dwarfism and in some cases of obesity, such as are usually designated Frohlich's syndrome, positive reactions have occurred suggesting that the gonadal failure present could not be due to deficiency of gonadotrophic hormone production and must be secondary to other causes.

Positive tests may be present in hyperthyroidism, diabetes mellitus and adrenal cortex hyperfunction either of the functional type or in cases of adrenal cortex tumor. Gonadal damage in either sex may cause a positive test; thus positive reactions are frequent at the menopause and in women with functional ovarian deficiency, ovarian tumors or inflammation. Positive reactions are also seen in men with testicular deficiency, cryptorchism and prostatic hypertrophy. Positive tests have been found also in alopecia areata and in cases of progressive myopia and keratoconus.

### Vitamin B<sub>1</sub>

The relation of vitamin B<sub>1</sub> to the reproductive cycle has been the subject of investigation of Williams, Griffith and Fralin.<sup>35</sup>

The requirements for this vitamin are definitely increased in pregnancy, although the effects of an outstanding deficiency, beriberi, on pregnancy have long been recognized in the Orient. Many subclinical deficiencies in this part of the world have been mislabeled as direct results of the gestation itself.



Many workers in the fields of nutrition have shown that the average American diet provides an insufficient margin of safety against beriberi prevention.

Not only have the toxemias of late pregnancy been explained on a theoretical basis of vitamin B<sub>1</sub> deficiency, but, practically, in the Orient they have been shown to be amenable to vitamin B<sub>1</sub> therapy.

From a study of the food records, Williams showed that one-third of a group of 91 pregnant women were not receiving an adequate amount of vitamin B<sub>1</sub>, calculated on a ratio of 15 international units per 100 Calories. Practically two-thirds of this group were receiving less than 500 units of vitamin B<sub>1</sub>. There was some positive correlation between the inadequacy of the intake and deficiency symptoms, such as excessive nausea and vomiting, fatigue and paresthesias.

## PUERPERIUM

### Acute Inversion

The treatment of acute inversion of the puerperal uterus based on an analysis of 21 cases is discussed by Harer and Sharkey.<sup>36</sup> The authors believe that the inverted uterus should be replaced immediately by *gentle taxis* when the patient is seen shortly after the inversion has occurred. Active *antishock treatment* should at the same time be started by an assistant and continued until the patient has reacted well.

If there is a tendency toward constriction of the cervix, this may be overcome and the replacement of the uterus facilitated by the intramuscular injection of from 0.5 to 1 cc. of solution of *epinephrine hydrochloride* 1:1000. The results of immediate manual replacement of the uterus have been very satisfactory. In a total of 13 cases there

were 11 recoveries and 2 deaths. One death occurred in a case in which inversion complicated eclampsia. The other death occurred as a result of recurrence of the inversion 3 hours after its first replacement. In this case the attending physician did not arrive at the hospital until more than an hour after the recurrence of the inversion and it was then found to be impossible to replace the uterus.

If the attending physician is not competent to replace an inverted uterus and a consultant must be called, considerable time may elapse before his arrival. In such cases he is likely to find the patient in profound shock and greatly exsanguinated. On examination of such a patient the cervix is found to be so constricted as to make replacement of the uterus extremely difficult or impossible. Obviously, such a patient is an extremely poor risk for any operative procedure and so all efforts should be directed toward the control of bleeding and the combating of shock. The hemorrhage may be minimized by *pushing the inverted uterus up into the vagina and packing around it with sterile gauze*. *Intravenous dextrose* or *acacia* followed as soon as possible by *blood transfusion*, the application of *external heat* and the administration of *morphine sulfate* and *cardiac stimulants* may be sufficient to overcome the shock.

In one of the cases in this series in which no attempt was made to replace the inverted uterus but in which all other treatment, including blood transfusion, was used, the patient died in 3 hours. In another case after moderate but unsuccessful effort at replacement of the inverted uterus death occurred within 2¾ hours. These patients were all in deep shock and markedly exsanguinated. In

3 cases of intermediate replacement the uteri were replaced with great difficulty and all 3 patients died. In another case the uterus was replaced manually after an interval of 11 hours during which time active antishock treatment was carried out. In this case death occurred 6 hours after replacement of the uterus.

In all cases of *chronic inversion* of the uterus, manual replacement is impossible. In such cases treatment must be effected by surgical means. Replacement of the uterus in these cases may be effected vaginally by *Küstner's operation* or by the better known *Spinelli modification*. In this operation the constricting ring of cervix is incised in the midline anteriorly. The uterus is reinverted and the uterine incision then repaired as in an anterior vaginal hysterotomy. Huntington advocates the abdominal approach for reinversion of the uterus. In his method the abdomen is opened by a midline incision below the umbilicus. The uterus is then replaced by grasping the invaginated portion with strong vulsellum forceps on opposite sides of the rim and pulling it up in a hand-over-hand fashion. After complete replacement of the uterus it is packed vaginally.

Two of these patients were treated by operative means. In 1 case a laparotomy under ethylene anesthesia was done 5 hours after inversion and the uterus replaced by the method of Huntington. The patient died 2 hours later. In the other case the condition was diagnosed as a pedunculated fibroid and a laparotomy was done for hysterectomy. When the peritoneal cavity was opened it was found that the uterus, which had actually been inverted, had been replaced in the process of packing the vagina prior to operation. Hysterectomy was done and on examination of the

excised uterus no fibroid was found. This patient recovered.

**Epinephrine Hydrochloride**—Epinephrine hydrochloride has been particularly useful in prolonged labor with contraction ring. It relaxes the uterine muscle, usually after 1 contraction, even in the presence of solution of posterior pituitary or ergotamine tartrate. Daro, Heskett and Schiller<sup>37</sup> report 3 successful cases in which this drug was used for acute puerperal inversion of the uterus.

In cases of inversion of the uterus, epinephrine has been used for treatment of the accompanying shock in insufficient doses to relax the uterus adequately. Its use in the treatment of shock probably precedes attempts to replace the uterus by too long an interval to be efficacious.

If there is disagreement in the literature as to the etiology of this condition, there seems to be almost uniform agreement as to the immediate treatment in acute cases. Nothing radical should be done before the shock is treated and no attempt to replace the uterus should be made until the patient is in better condition, except to place the uterus in the vagina and pack and apply a pad with pressure to help control hemorrhage.

The authors conclude from their 3 cases that if inversion occurs, it can probably be corrected immediately, before shock occurs, by adequate doses of epinephrine hydrochloride, namely, 15 minims (1 cc.), repeated if necessary.

### Lactation

**Inhibition with Stilbestrol** -- The use of stilbestrol in a series of 75 puerperal women for the purpose of inhibiting or suppressing lactation is reported by Muckle.<sup>38</sup> One-twelfth grain (5 mg.) of stilbestrol administered 3 times a day for a total of 6 doses relieved the breast engorgement, and decreased or pre-

vented lactation in every case. In 40 per cent of 53 patients followed, there was a secondary recurrence of lactation. This was usually painless and slight in amount. Only 2 patients were nauseated in a series of 75 women receiving stilbestrol. The author feels that the use of stilbestrol is an efficient and safe method of suppressing lactation early in the puerperium.

### Newborn

**Hemorrhage and Vitamin K**—Beginning September 1, 1939, every other patient in labor admitted to the Johns Hopkins Hospital was given vitamin K by mouth. The preparation used was 2-methyl-1, 4 naphthoquinone, in a single dose of  $\frac{1}{30}$  grain (2 mg.)

As of May 1, 1940, 384 mothers had received vitamin K in labor, while the alternate control series numbered 392. The 2 series were similar in every respect, the distribution of patient according to race, parity, contracted pelvis, operative incidence, and premature labors, being approximately the same in the 2 groups. The results are reported by Helman, Shettles and Eastman.<sup>39</sup>

Most fundamental is the fact that present-day plasma prothrombin studies have given us a new conception of hemorrhagic diathesis in the newborn. Far from being a disease entity unto itself, it represents simply an extreme degree of a condition, hypoprothrombinemia, which all newborn infants exhibit to a certain extent and in various gradations. Unless the plasma prothrombin level is extremely low, this hypoprothrombinemia may be without clinical manifestations. However, if birth trauma, anoxia, and other causes of bleeding are superimposed upon it, this prothrombin lack must necessarily play a part in the duration, and, therefore, in the extent of the bleeding. Along with trauma and

anoxia, then, hypoprothrombinemia must be regarded as a factor in the outcome of every case of bleeding in the newborn, whether cerebral or otherwise; and it is the 1 factor in this triad, let it be recalled, which is subject to prophylactic correction.

To what extent will the routine antenatal administration of vitamin K diminish hemorrhage in the newborn and thereby reduce neonatal mortality? The authors believe, in the first place, that such a practice, properly timed and with suitable dosage, will well-nigh eliminate so-called hemorrhagic disease of the newborn. In the second place, the facts indicate that certain types of cerebral hemorrhage, particularly small hemorrhages which ooze over a number of days, may be preventable by this procedure. To what slight extent the elimination of such deaths would diminish neonatal mortality, it is obviously impossible to state, but the evidence presented would seem of sufficient promise to warrant recommending the routine antenatal administration of vitamin K for trial.

### Responses of the Human Post-partum Uterus to Posterior Pituitary Extracts

In a study of the response of the human post-partum uterus Gardiner and Bradbury<sup>40</sup> found that when posterior pituitary extracts are given intravenously to combat post-partum hemorrhage, the initial tetanic contraction of the uterus may be anticipated within 10 to 20 seconds. While uteri vary in their degree of response to posterior pituitary extracts, the induced activity usually lasts for a period of about 30 minutes. Subsequent intravenous doses are less effective than the first. Failure of the post-partum uterus to contract after the intravenous administration of 5 minims

(0.3 cc.) of posterior pituitary extract should be regarded as a grave sign and preparations for more active treatment of the uterine atony should be made without delay. It has been their experience that patients who fail to respond to the intravenous injections of posterior pituitary extracts usually require intra-uterine packing to control post-partum bleeding.

Pitocin rather than pituitrin should be employed in patients with potential or actual toxemia of pregnancy to minimize the possibility of "pituitary shock," which may be caused by the pressor factor present in pituitrin.

### Sepsis

Advances of the last 2 decades in the knowledge of puerperal infection are summed up by Watson.<sup>41</sup> These are as follows:

1. Recognition of the part played by the anaerobes in puerperal and post-abortion infection.

2. Proof that these anaerobic infections are endogenous in origin.

3. Proof that such infections are predisposed to by shock, hemorrhage, prolonged labor and traumatization of tissue.

4. Realization that the removal of dead and decomposing material resulting from this type of infection can, in most instances, be effected with no risk, and usually with great benefit to the patient.

5. Identification of different groups of the beta hemolytic streptococcus and proof that only Group A is virulent in the human subject.

6. Establishment of the fact that infection with this organism is practically always exogenous.

7. Proof that these organisms are usually conveyed to the patient by a carrier who harbors them in mouth, nose or throat.

8. Demonstration of the fact that the risk of infecting patients is practically annulled by periodic nose and throat culture of all the members of the obstetric staff and elimination of those who are carriers, and by the complete masking of the nose and mouth of all those who are attendant upon the parturient and puerperal woman.

9. Demonstration of the persistence of the organisms in the environment of an infected individual even for long periods after her removal therefrom.

10. A recognition of the necessity for most complete isolation of all such infected individuals and for proper provision for this in every maternity service.

11. The discovery of the beneficial effects of sulphanilamide and its derivatives in streptococcal, gonococcal and *Bacillus coli* infections.

### Sterilization

Post-partum sterilization is discussed by Hewitt and Witley.<sup>42</sup> One hundred cases of tubal ligation done 1 hour after delivery on patients who delivered spontaneously are reported. There was no mortality and a 2 per cent morbidity. To date they have not had any failures reported.

Post-partum sterilization, the authors claim, offers an economical means of sterilization from the standpoint of hospitalization, as it does not prolong the stay in the hospital and does not give the patient any discomfort as does the average pelvic operation. The time consumed in the operation is short, averaging 15 minutes.

The authors feel that 1 hour after delivery is the best time for it to be done, because the fundus is even with the umbilicus and they have less difficulty in exposing the tubes than they would if they waited a few days longer. If the uterus is not manipulated too

much, the bleeding during the operation will be small. Involution of the uterus was not retarded. The technic of the operation was as follows:

All of the patients were selected from those who had had spontaneous deliveries and no contraindications to operation. Immediately following delivery the patient was given  $\frac{1}{4}$  grain (0.016 Gm.) of *morphine* and  $\frac{1}{150}$  grain (0.45 mg.) of *atropine*. The abdomen was prepared for operation and the patient sent to the operating room 1 hour after delivery. In about one-half of the cases the authors used *cyclopropane-gas anesthesia* and in the other one-half they used ether. An incision  $1\frac{1}{2}$  inches long was made immediately below the umbilicus, and the uterus was pushed to one side, bringing the tube into the incision. The tubes were picked up about the middle third and a large loop was crushed in 3 places. Each crushed place was tied with a linen suture inserted through the mesosalpinx. This is somewhat different from the Madlener technic where a small loop is used and crushed in 3 places but tied in 2. The postoperative orders are the same as the routine post-partum orders, that is giving a *regular diet* and *enema* on the third day, and rarely, if ever, do the patients require any opiates other than *codeine* and *aspirin* for afterpains.

### Effects of Stilbestrol

Diethylstilbestrol was administered to 200 puerperal women by Connally, Dann, Reese and Douglass,<sup>43</sup> in an attempt to show the effects of estrogens on the post-partum uterus with special reference to endometrial regenerations.

In this group of women no case under observation showed any single toxic side effect, even though the drug was pushed to more than the usual therapeutic dose. From clinical observation

only, these uteri sensitized by the drug apparently responded more readily to oxytocics than those in the control group.

Lactation was apparently suppressed in 70.5 per cent of the cases observed. However, in the dosage used complete inhibition was not noted, although the onset of lactation was delayed longer than in the control group. No incidence of engorged or painful breasts was noted in the treated group. Clinically the flow of lochia was not materially changed. Stilbestrol apparently had no immediate effect on early involution of the puerperal uterus; however, pelvic examinations on about the twenty-first post-partum day revealed a more rapid involution than occurred in the control group.

It was noted from the clinical standpoint that the morbidity in treated patients was materially affected, being 4 per cent as against a total morbidity of 12.8 per cent for the year 1939. Since their series included only operative cases, it would be supposed that the morbidity rate would be higher than the 12.8 per cent figure for 1939, which included normal as well as operative deliveries.

### Post-partum Urinary Suppression

Post-partum urinary suppression resembling bilateral cortical necrosis of the kidneys is discussed by Madding, Binger and Hunt.<sup>44</sup> The authors report a case with the following features:

(1) Fetal death apparently from abruptio placentae as evidenced by the mild toxemia and severe post-partum hemorrhage from uterine atony, (2) typical anuria nearly complete for 8 days, (3) clear mental condition of the patient and freedom from symptoms, except nausea and vomiting, in spite of marked nitrogen retention, (4) usual observations in the blood and urine and (5) lack of any urologic lesion to ex-

plain the anuria or tangible toxemia other than the factor of pregnancy.

The prognosis in this rare condition is grave; in 63 of the 75 cases reported to date death has occurred, a mortality of 84 per cent. In borderline cases such as the one reported, various supportive measures may make the difference between recovery and death.

The authors maintain these patients should be treated in the same manner as any patient who has acute nephritis with oliguria. It is important to keep the patient warm; *hot packs* applied over the renal areas, if tolerated, are advisable. Even though edema is present fluids should be administered liberally. Usually nausea and vomiting are complicating factors and it is necessary to give fluid intravenously. Preferably 1 pint (500 cc.) of a 20 per cent solution of *dextrose* together with  $2\frac{1}{2}$  drams (10 cc.) of *aminophylline* or 1 quart (1000 cc.) of 10 per cent dextrose with  $2\frac{1}{2}$  drams (10 cc.) of aminophylline given morning and afternoon. The total intake of fluid should be between 2 and 3 quarts (2000 and 3000 cc.) a day.

Studies of the carbon dioxide combining power, blood urea, creatinine and chlorides should be done. There is a tendency in these cases toward acidosis, which in turn impairs renal function. If the carbon dioxide combining power falls to 40 per cent or less, the administration of 1 pint (500 cc.) of a 5 per cent solution of *sodium bicarbonate* intravenously is advisable and should be repeated daily until the carbon dioxide combining power is elevated to 50 or 60 volumes per cent. Once this level is reached, it usually can be maintained by the administration of 10 grains (0.65 Gm.) of sodium bicarbonate 3 times a day by mouth. If hemolysis is present, hematin is precipitated in the tubules of the kidney in an acid medium. Hematin

is soluble in an alkaline medium and thus may be dissolved to restore tubular function and urinary excretion.

Limit the intake of protein to 40 or 50 Gm. a day. The use of diuretics such as potassium nitrate, ammonium chloride or ammonium nitrate is not advisable until diuresis has begun, and even then such compounds are of questionable value. Once this type of kidney begins to function, the prognosis is good. Often in such instances credit is given the diuretic agent when really the natural processes of recovery of the kidney have accounted for the improvement. Certainly the more powerful mercurial diuretics are contraindicated and could well destroy all recovery that is taking place. If the patient has become very anemic, *transfusions* may be tried. However, they should be given in small amounts and cross agglutination of the donor's blood directly with that of the recipient should be performed. Usually, it is conceivable that enough blood could be lost through hemorrhage to lower the concentration of protein in the serum to 5 per cent or less, resulting in a decreased colloidal osmotic pressure, which would produce further retention of fluid, oliguria and edema. If the concentration of serum proteins is less than 5 per cent and if it is found that a low colloidal osmotic pressure is a factor in inhibiting urinary output, a solution of acacia may be given intravenously. One pint (500 cc.) of a 6 per cent solution of *acacia* can be given daily or on alternate days until 3 pints (1500 cc.) (a total of 3 ounces—90 Gm.—of acacia) have been given.

Decapsulation is too hazardous and offers too slight an advantage to be attempted. Added trauma, anesthetic agents and other factors do more harm than good. If the toxic or infectious process in the kidneys is not too over-

much, the bleeding during the operation will be small. Involution of the uterus was not retarded. The technic of the operation was as follows:

All of the patients were selected from those who had had spontaneous deliveries and no contraindications to operation. Immediately following delivery the patient was given  $\frac{1}{4}$  grain (0.016 Gm.) of *morphine* and  $\frac{1}{150}$  grain (0.45 mg.) of *atropine*. The abdomen was prepared for operation and the patient sent to the operating room 1 hour after delivery. In about one-half of the cases the authors used *cyclopropane-gas anesthesia* and in the other one-half they used ether. An incision  $1\frac{1}{2}$  inches long was made immediately below the umbilicus, and the uterus was pushed to one side, bringing the tube into the incision. The tubes were picked up about the middle third and a large loop was crushed in 3 places. Each crushed place was tied with a linen suture inserted through the mesosalpinx. This is somewhat different from the Madlener technic where a small loop is used and crushed in 3 places but tied in 2. The postoperative orders are the same as the routine post-partum orders, that is giving a *regular diet* and *enema* on the third day, and rarely, if ever, do the patients require any opiates other than *codeine* and *aspirin* for afterpains.

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## IMMUNOLOGY

*Edited by* ARTHUR F. COCA, M.D.

### BACTERIAL TOXINS

*By* ARTHUR LOCKE, Ph.D

**Physiological Effect**—Interest is increasing in the chain of events produced in the body, by the bacterial toxins in sublethal dosage. Changes in glucose tolerance and in extent of vitamin C reserve<sup>1</sup> have been found which, in turn, exert secondary effects on metabolism, function, and structure.

It has not been possible to prevent the direct, primary effects of the true toxins other than through administration of specific antitoxins. The secondary effects may prove to be reversible to the extent indicated by the observations of King, Musulin and Swanson<sup>2</sup> on the influence of change in level of vitamin C intake on the degree of tooth injury produced by diphtheria toxin in the growing guinea-pig. These investigators found injuries to the odontoblasts and dentin following injection of 0.4-0.8 MLD of diphtheria toxin in guinea-pigs receiving daily feedings of 0.8 mg. of vitamin C. Comparable injury was produced, without toxin-injection, by reducing the vitamin C in-

take from 0.8 to 0.5 mg. per day. No injury was produced, even after toxin injection, following increase in the vitamin C intake to 5 mg. per day. The toxin injection, in itself, produced vitamin depletion. Correction for this primary effect through increased vitamin intake prevented the secondary effect on tooth structure.

**Sulfonamides and Toxin-production**—The sulfonamides have not been observed to prolong life or reduce mortality following administration to animals given a minimum lethal dose of diphtheria or tetanus toxin.<sup>3-5</sup> They have been observed to exert bacteriostatic action against infections by toxin-producing organisms.<sup>4, 6-8</sup> Clinically, a checking of toxin-production at its source—through prevention of the growth of the toxin-producing agent—is as important as the equally necessary neutralization, destruction, or counteraction of such toxin as may already have become disseminated.



Many of the pathogens produce toxic substances less well characterized than diphtheria and tetanus toxin and requiring injection in from 1000 to 10,000 times greater amount to produce death. These substances are of importance to the extent that they participate in the effects produced by the associated infection. Two groups of investigators have reported the saving of mice given a minimal lethal dose of this type of toxin,

through subsequent sulfonamide administration.<sup>9, 10</sup> Other groups have failed to observe such effect<sup>5, 11</sup> The divergence in results was possibly a consequence of the low intrinsic toxicity and lack of entire reproducibility of the preparations tested.

Sulfanilamide in massive dosage has been shown to confer nonspecific protection to the rabbit against histamine-shock.<sup>12</sup>

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## IMMUNIZATION AGAINST RABIES

By R. A. KELSER, D.V.M., Ph.D

During the past several years there has been a great amount of discussion and debate with reference to the efficacy of rabies vaccines, especially the so-called "killed virus" type. Much of this has concerned the vaccination of dogs by the single dose method, but in addition doubt has been cast upon the value of "Pasteur treatment" in preventing hydrophobia in the human family.

Experience from the world-wide use of the "Pasteur treatment" in preventing hydrophobia in exposed persons is such as to make untenable the suggestion that it lacks value.

While the vaccination of dogs by no means insures protection in all cases, the procedure does prevent the development of the disease in many animals. Further, additional evidence has been brought forth to indicate that chloroformized vaccines are superior to phenolized preparations.

Webster,<sup>13</sup> while concluding from his investigations that vaccination against rabies with available vaccines was generally of little or no value, nevertheless in his own experiments found that both mice and dogs could be consistently immunized with chloroformized vaccine when given in sufficient dosage. Results

with phenolized vaccines were negative.

Recent reports by Leach<sup>14</sup> indicate excellent results in the immunization of dogs with chloroformized rabies vaccine. In 1 experiment, in which 50 dogs were given a single subcutaneous injection of 5 cc. of chloroform-treated vaccine, only 4 per cent succumbed to rabies following an intramuscular dose of street virus. Of 55 control dogs, 61.8 per cent succumbed to the disease.

In vaccinating dogs against rabies it is believed that, whenever possible, multiple rather than single doses of vaccine should be given. The administration of 3 doses of vaccine, a week apart, is much preferable to the single dose. A reasonable increase in dosage over the conventional 5 cc. might well be considered for the larger breeds of dogs.

In employing rabies vaccine, owners of dogs should be made to understand clearly that while vaccination definitely lessens the chance of their animals developing rabies if exposed to the disease, it is by no means a guarantee that infection is impossible.

Canine rabies vaccination cannot serve to replace well-recognized regulatory measures for the control of rabies nor to justify laxity in enforcement of same.

The vaccination procedure must be considered only an adjunct to these measures. Further, the vaccination of dogs should not be placed on a compulsory basis. When any vaccination procedure is made compulsory, the public inference is that it is so nearly perfect in preventing the particular disease as to justify its mandatory use in a community. Unfortunately, this cannot as yet be said of canine rabies vaccination.

A considerable step forward has been made in the development and use of the *mouse protection test* for determining potency of rabies vaccines. This test is now required of manufacturers of rabies vaccines. While results with the test may not be indicative of precisely what can be accomplished with a given lot of vaccine in species other than the mouse, it does give valuable information as to antigenicity.

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## SERUM DIAGNOSIS OF SYPHILIS BY PRECIPITATION

By REUBEN L. KAHN, M.S., Sc.D.

A new type of precipitation procedure has recently been added to the armamentarium of the serodiagnosis of syphilis. The procedure is referred to as *verification test* and its function is to aid physicians in the detection of false positive reactions given by any of the serodiagnostic precipitation and complement-fixation tests in present day use. The problem of false positives is associated with the diagnosis of latent asymptomatic cases of syphilis. In these cases, the vast majority of seropositive reactions are unquestionably due to syphilis. But those positive reactions not due to this disease could not heretofore be detected by means of a laboratory procedure; hence, the verification test.<sup>15, 15a</sup>

**Experimental Approach** — In attempting to detect false positive serologic reactions in human beings, studies were first directed to the differentiation between positive reactions given by apparently normal animals and by known cases of syphilis. These studies led to the observation that the standard Kahn test carried out at various temperatures provides a means for this differentiation. If serums from syphilitic persons and from apparently normal animals are examined with this test in the usual man-

ner, at 21° C., the precipitation reactions appear identical. If, however, the same serums are examined at 37° C. and at 1° C., differences in the precipitation results become manifest. At 37° C., syphilitic serums show a tendency toward marked precipitation, and animal serums, toward little or no precipitation. At 1° C., syphilitic serums show a tendency toward little or no precipitation, and animal serums toward marked precipitation.

In the case of serums giving strongly positive reactions with a diagnostic test, differences in the degree of precipitation may not be demonstrated by temperatures of 37° or 1° C., unless the serums are first diluted with physiologic solution of sodium chloride. The extent of dilution necessary is determined by the quantitative Kahn test. After the reactions of the serums are thus reduced from strongly to weakly positive, the differences in the results at the 2 temperatures become evident.

Table I gives illustrative examples of the behavior of syphilitic human serums and nonsyphilitic animal serums in the 3-tube Kahn test carried out at 37° and 1° C.

TABLE I

Serum Number	Results with Sero-diagnostic Test	Precipitation Results					
		37° C			1° C		
		Tube 1	Tube 2	Tube 3	Tube 1	Tube 2	Tube 3

Serologically positive serums from syphilitic persons give more marked precipitation at 37° than at 1° C

1	Positive	++++	++++	++++	—	±	++
2	Positive	+	++++	++++	—	—	—
3	Positive	—	++	++++	—	—	±
4	Doubtful	—	++	++++	—	—	—
5	Doubtful	±	+	+++	—	—	±
Control	Negative	—	—	—	—	—	—

Serologically positive sera from lower animals (horses, pigs, chickens, etc.) give more marked precipitation at 1° than at 37° C

1	Positive	—	—	—	++++	++++	++++
2	Positive	—	—	—	++++	++++	++++
3	Positive	—	—	+	++	+++	++++
4	Doubtful	—	—	±	—	+++	++++
5	Doubtful	—	—	—	±	+	+++
Control	Negative	—	—	—	—	—	—

**Seropositive Reactions in Non-syphilitic Human Beings**—Serologically positive serums from nonsyphilitic human beings with malaria were found to give with the differential temperature procedure reactions similar to those given by serologically positive serums from lower animals. A group of syphilis-free mental patients were inoculated with malaria and their serologic response studied before, during, and after malarial paroxysms. A number of these patients gave positive serologic reactions with diagnostic tests. When examining these serologically positive serums with the differential temperature procedure, stronger precipitation reactions at 1° than at 37° C. were obtained.

With regard to leprosy, the results of the differential temperature procedure were not found to be conclusive. Approximately two-thirds of seropositive leprosy cases gave more marked precipitation at 1° than at 37° C., the remaining

third gave more marked precipitation at 37° than at 1° C. Unfortunately, it was difficult to establish with certainty that the cases which gave the syphilitic type of reactions had syphilis in addition to leprosy and the cases which gave the animal type of reactions were free from syphilis. Practically all the leprosy patients denied syphilitic infection, and the lesions in many instances did not aid in differentiating between leprosy and syphilis. The group of serums which gave the syphilitic type of reactions showed relatively high quantitative Kahn titers, while the group which gave the animal type of reactions showed low quantitative titers.

The differential temperature technic was also applied to numerous seropositive cases in which clinical studies pointed to absence of syphilis. In most of these cases, more marked precipitation at 1° than at 37° C. were obtained. In a small number of cases, the

results with the differential temperature technic were inconclusive.<sup>16</sup>

These observations led to the view that there exist 2 basic types of seropositive reactions, *i. e.*, (1) a syphilitic type, associated with syphilis, and (2) a general biologic type, relatively widespread among lower animals and to a lesser degree among human beings, in the absence of syphilis.

**Potentialities for False Positives in Human Beings**—Nonsyphilitic persons giving negative serologic reactions with diagnostic tests may possess potentialities for giving false positive serologic reactions. When serums from routine hospital patients giving seronegative reactions were subjected to re-examination with the differential temperature technic at 37° C. and at 1° C., about 4 per cent were found to give some precipitation at 1° C. and no precipitation at 37° C. About 50 per cent of patients with leprosy and malaria giving negative serologic reactions with diagnostic tests gave reactions at 1° C. It is believed that these reactions presage positive reactions with diagnostic tests and that nonsyphilitic seronegative persons giving these reactions in the cold may become seropositive under certain conditions.<sup>16a</sup>

**Practical Application**—The differential temperature technic, under the term *verification test*, is recommended by the author (Kahn) as an aid in the detection of false positive serologic reactions in the diagnosis of asymptomatic and questionable cases of syphilis. The verification test is not recommended to take the place of serodiagnostic tests,

but is to be used as a supplementary procedure to these tests. It is not intended to be used for the verification of all positive reactions given by serodiagnostic methods, but only to verify those reactions suspected of being false positives.

In utilizing the verification test as an aid in the diagnosis of questionable cases, it is of importance to repeat the test after several weeks. In some instances additional repeat examinations at various intervals may be necessary. Interval retesting throws greater light on the question of true and false positives than immediate retesting.

#### **Types of Verification Reactions**

**Noted**—There are 3 types of verification reactions obtained with serums giving positive results with serodiagnostic tests:<sup>17</sup>

1. *Syphilitic type*—when precipitation is more marked at 37° than at 1° C.—most commonly noted
2. *General biologic type*—when precipitation is more marked at 1° than at 37° C.—noted infrequently
3. *Inconclusive type*—when results cannot be classified under either 1 or 2—noted infrequently

Serums giving negative results with a serodiagnostic test may in some instances show precipitation with the verification test. Types of verification reactions observed with serums giving negative results with serodiagnostic tests:

1. *Negative type*—when no precipitation occurs at either 37° or 1° C.—most commonly noted.
2. *General biologic type*—noted infrequently.
3. *Syphilitic type*—generally in treated cases of syphilis—noted infrequently.
4. *Inconclusive type*—noted infrequently.

## DIAGNOSIS BY THE METHOD OF COMPLEMENT FIXATION

By AUGUSTUS BALDWIN WADSWORTH, M.D., and ELIZABETH MALTANER

The recognition of the importance of quantitative determination of specific activity in serologic tests and the recent development of practical quantitative methods in the procedure of complement fixation, together with comparative series of tests conducted under the auspices of the *United States Public Health Service*, have stimulated the investigation of the different methods of serologic tests, chiefly as they are related to the diagnosis of syphilis, but also as applied to other diseases, in particular, the virus infections.

### Syphilis

**Antigens**—Progress has been made in the investigation of the antigenic activity of alcoholic extracts of beef heart. Separation of inactive, anticomplementary, and specifically active fractions has been obtained by different methods. Balbi<sup>18</sup> adsorbed tissue extracts on aluminum hydroxide, and on earths, such as bentonite and floridin, and elutriated with alcohol, along the lines of the studies by O. Fischer. Pangborn<sup>19</sup> by a modification of the cadmium chloride method of separation obtained a serologically active acetone-insoluble substance. It is as yet difficult to ascertain the practical significance of the results of this work and, especially, to determine which substances are active and which inert; for example, the lecithin appears essential to the activity of the fraction, but pure lecithin is inert. Hence, further analytical study must be made of the relationships of the essential active substances to the lipids present in the antigen as it is used in the test.

In the light of these studies of the antigenic fractions of beef-heart antigen, it is difficult to evaluate the practical

significance of the work of Beck<sup>20</sup> and Eagle and others<sup>21, 22</sup> on the activity of antigens prepared from the spirochete and especially in view of previous work in this field in which extracts prepared from cultured spirochetes failed to react with syphilitic sera or reacted to approximately the same degree as similar preparations from the uninoculated culture medium.

Kent<sup>23</sup> has demonstrated that there is an optimum ratio of cholesterol to tissue extract for use as antigen in the complement-fixation test for syphilis and described a simple quantitative method for determining it.

**Standardization of Test**—An assembly of laboratory directors and serologists was held in 1938 under the auspices of the *Committee on Evaluation of Serodiagnostic Tests for Syphilis* and the *United States Public Health Service*. The discussions centered on means for improving test performance. The necessity for adherence to standard technics was emphasized, as well as the responsibility of serologists for making accurate descriptions of methods readily available. Recommendations were made in regard to methods of conducting serologic surveys, the training of personnel, and the problem of licensing or approving laboratories.<sup>24</sup> The results of tests performed in State laboratories in 1938 and 1939 indicate continued improvement in performance. Most of the laboratories still reporting unsatisfactory results are taking steps to improve them.<sup>25</sup> Comparative evaluation of results on a percentage basis is difficult and the methods adopted by the Committee have been discussed in a special report which suggests that the evaluations should be based on complete clin-

ical and serologic data in each case, without any abridgment of the fundamental information.<sup>26</sup> Certainly in the light of present knowledge no serologic test for syphilis can be considered to possess 100 per cent specificity.

Laboratory administration as it relates to the serology of syphilis has been discussed in a practical way by Mahoney and Harrison,<sup>27</sup> who have outlined what is reasonable to expect in regard to test performance on the basis of present knowledge of serology. The *United States Public Health Service* has again published the latest modifications in technic of the tests taken as "controls" in their evaluation studies.<sup>28</sup> Some of the problems of interpretation of serologic tests in syphilis and the need for standardization have been considered in a recent paper by MacNabb and Matthews.<sup>29</sup> In their experience the difference between standard and oversensitive methods lies in the fact that the latter yields a greater number of "positive" results, principally in latent cases, and has a somewhat lower specificity. Reporting the results of quantitative tests on all specimens that react affords the laboratory an opportunity of rendering valuable service to the clinician and the patient.

Reports of misleading reactions in the test for syphilis with sera from tuberculous and other infections must be reviewed critically. Parren and Emerson<sup>30</sup> noted reactions with sera from tuberculosis that were of doubtful significance. Similar results have been reported with sera from cases of leprosy. The doubtful significance of these reactions becomes more apparent when quantitative methods of titrating the specific activities of these sera are used in the comparative evaluation, as in the papers by Maltaner,<sup>31, 32</sup> which also include comparison of the activity of sera from yaws.

Although the reactions of sera from yaws and syphilis correspond very closely, it is evident that this is not true of leprosy if the complement-fixation test with beef-heart antigen is properly standardized and controlled. The numerous reactions recorded by Kitchen, Webb, and Kupper<sup>33</sup> in nonsyphilitic patients with functional psychoses following the administration of malarial therapy are also interesting in this connection. While other reports<sup>34</sup> indicate that infectious mononucleosis should be included in the category of infections in which misleading reactions occur, personal experience has shown that specimens from patients with this disease may be anticomplementary but have very seldom been found to react in serologic tests for syphilis.

Although reactions undoubtedly may occur in some instances in complement-fixation tests for syphilis in the absence of syphilitic infection, much of the present confusion in this field can be attributed to the use of oversensitive methods with antigens in which the anticomplementary and nonspecific activities have not been reduced to a minimum; also to the failure to determine accurately the degree of reaction in such tests with original and confirmatory specimens. Comparative studies of precipitation and complement fixation with incubation at 37° C. and at low temperatures have long interested serologists. Personal experience with precipitation has shown that incubation at 37° C. eliminates certain discrepant reactions when compared with complement fixation and incubation at 37° C. occasionally demonstrates complement fixation in the very early stages of syphilis when reaction fails to occur or is less marked at low temperatures. The question of the significance of these and other irregular slight reactions has been and continues to be as yet indeterminate. Kahn<sup>15</sup> as the result of recent

painstaking comparisons of precipitation at incubator and refrigerator temperatures has suggested a differentiation of specific and nonspecific reactions on the basis of such tests.

*Referees on the Serodiagnosis of Syphilis for the Committee on Diagnostic Procedures and Reagents of the Laboratory Section, American Public Health Association*, Gilbert and Maltaner, in their report define the principles governing the standardization of reagents and the minimum requirements of technic to which any test for the serodiagnosis of syphilis chosen for use at the present time should be expected to conform.<sup>35</sup> The development of methods of determining the complement-fixation reaction quantitatively has clarified the relationships governing the various steps in the procedure and has provided a sound basis for the standardization of the test and for comparative serologic study.

**Technic**—The technic of the quantitative complement-fixation test is described in a new edition of *Standard Methods of the Division of Laboratories and Research of the New York State Department of Health*<sup>36</sup> in greater detail than has been given previously in this Cyclopedia. The minutiae of the test are now reproduced on page 160. The technic of determining the optimum ratio of cholesterol to tissue extract as described by Kent<sup>23</sup> is included, as well as the method for determining titers that lie outside the range of the abbreviated routine test.

### Other Diseases

While progress has been made in complement-fixation studies in the bacterial, virus, and other infections, and many of the reports are important in themselves, further study appears necessary in most instances to establish their significance in the broad field of diag-

nosis and prognosis by complement fixation.

Studies of chemical fractions of the *tubercle bacillus* have been continued.<sup>37-41</sup> An antigenic protein fraction in tests with a small group of sera appeared to differentiate infections due to human and bovine strains.<sup>42-43</sup> The results with an antigen prepared from tubercle bacilli grown under conditions that render them nonacidfast have been reported.<sup>44</sup> A procedure of "reactivation" has been described: Following the intracutaneous injection of tuberculin, reactions appeared in the sera in 66 per cent of patients with active gland or bone tuberculosis, but not in nontuberculous persons with negative cutaneous reactions; since reactions also occurred in more than one-third of persons without clinical signs but with positive skin reactions, active and inactive disease was not clearly differentiated.<sup>45</sup> Further studies have been made of a "confirmation" reaction which is based on the specific absorption of antibody from serum by antigen adsorbed on koalin; antibody was almost completely recovered by elutriation in salt solution at a temperature of 59°-60° C.; reactivity of the serum associated with lability of the serum was not removed by adsorption on koalin-antigen sediments and was thus differentiated from specific activity.<sup>46</sup> A few reports might be mentioned that record the comparative findings in different stages or forms of the disease.<sup>47-50</sup> Comparative studies of the results of these methods with those of quantitative methods of titrating the specific activity would provide essential confirmation for evaluating their practical significance and diagnostic value.

The study of the complement-fixation reaction in *gonococcal infection* has been continued. Cohn<sup>51</sup> has reported on a series of cases that received sulfanilamide

therapy and were followed for a year or longer. The specificity of the complement-fixation reaction was not affected by sulfanilamide treatment. Cases with persistent clinical signs continued to react, while those which on the basis of clinical and bacteriologic evidence were regarded as cured underwent serologic reversal. Of 59 cases, 11 failed to react at any time in spite of the presence of active infection. Torrey<sup>52</sup> has stressed the importance of selecting strains of broad antigenic valance for use in preparing antigen. Rice<sup>53</sup> has reviewed the present status of work in this field and reported new observations on the activities, determined quantitatively with gonococcus antigens, of sera from cases with and without history or clinical evidence of gonococcal infection. While titers up to 2000 have been obtained in quantitative tests for syphilis and of 200 to 300 in tests for tuberculosis, titers over 50 have not yet been recorded for human sera with the gonococcal antigens used. An appreciable number of sera both from complicated and uncomplicated infections—from 35 to 64 per cent—had titers under 2.5, while 1.8 per cent of the sera from persons with other diseases had titers over 2.5. In the sera of healthy persons titers over 2.5 were not found. Further studies of antigens, as knowledge advances regarding the structure of the gonococcal cell, may improve the sensitivity and specificity of the test and enhance its practical value.

The recent reports of the application of the method of complement fixation in other infections should be mentioned; for example, in *helminthiasis*<sup>54, 55</sup> *Weil's disease*,<sup>56, 57</sup> *malaria*<sup>58-61</sup> *amebiasis*,<sup>62</sup> *whooping cough*,<sup>63</sup> *Brown-Pearce carcinoma*<sup>64</sup> and *virus-induced tumors of rabbits*<sup>65-68</sup> as well as in the virus diseases of *lymphogranuloma ve-*

*nercum*,<sup>69</sup> *psittacosis*,<sup>70, 71</sup> *lymphocytic choriomeningitis*,<sup>72-74</sup> *herpes and varicella*,<sup>75</sup> *foot and mouth disease*,<sup>76</sup> and *influenza*<sup>77, 78</sup>

Even this brief review indicates the importance of, and the active interest in, this ever-widening field of research on the practical application of complement fixation. Owing to the varied technical methods of complement fixation that are used, comparative evaluation of the results of different studies is difficult or frequently impossible. The use of quantitative methods that are now available and that have been simplified to an extent to make them practicable, even when relatively small amounts of material are available for study, would provide the essential basic control data for comparative evaluation.

### Technic of Quantitative Complement-Fixation Test for Syphilis\*

No changes have been made in the preparation of reagents except as indicated under standardization of antigen. (SEE p. 164.)

**Standardization of Reagents**—GENERAL DIRECTIONS—For measuring quantities of serum, antigen, or complement less than 0.1 cc., use a pipette of 0.2-cc. capacity graduated to 0.01 cc. For measuring quantities of from 0.1 to 1 cc., use a pipette of 1-cc. capacity graduated to 0.1 cc. For quantities of from 1 to 10 cc., use a 2-cc., 5-cc., or 10-cc. pipette. For quantities greater than 10 cc., use a 10-cc pipette or a suitably graduated cylinder.

For measuring 0.1-cc. or 0.2-cc quantities of reagents, pipetting machines have been found to provide increased accuracy and speed. The machines are run by electricity and are so adjusted that, with each stroke of a piston, exactly the desired quantity is delivered. The adjustment is checked each time the machine is used.

Do not take less than 0.1 cc. of fluid as the basis for any dilution. When only a small

\* From Wadsworth, A. B., *Standard Methods of the Division of Laboratories and Research*, New York State Department of Health, 2d Edit., Williams and Wilkins Co., Baltimore, 1939. Citations made by courtesy of the publisher.



TABLE VIII  
COMPLEMENT TITRATION

Tube No	Comple- ment (1 40)	Salt Solu- tion	Sensi- tized Sheep Cells	Period for Hemolysis
	cc.	cc	cc.	
1	0 13	0 17	0.2	15 minutes in the water bath at 37° C
2	0 12	0 18	0 2	
3	0 11	0 19	0.2	
4	0 10	0 20	0.2	
5	0 09	0 21	0 2	
6	0.08	0.22	0.2	
7	0.07	0 23	0.2	
8	0.06	0 24	0 2	
9	0 05	0 25	0 2	
10	0.04	0 26	0.2	
11	0.03	0 27	0.2	
12	0 02	0 28	0.2	

amount of a high dilution is required, as in titrating amboceptor, make a 1.100 dilution and prepare from that the higher dilution desired. Mix the diluted reagent thoroughly by pouring back and forth from 1 flask to another at least 3 times or, if there are only a few cubic centimeters of it, by drawing up in a clean 5-cc. or 10-cc. pipette at least 3 times.

In carrying out titrations or tests for which the directions are given in tabular form, pipette the reagents in the order indicated, beginning at the left. If the first reagent is to be measured in quantities of less than 0.1 cc., pipette it to the bottom of each tube. Pipette the other reagents from the top, and shake the rack after the addition of each reagent. Add the salt solution in such a way as to wash down any reagents that may have adhered to the side of the tube.

Shake the suspension of sheep red blood cells thoroughly before withdrawing portions for preparing sensitized cells or other purposes, in order to obtain representative samples. During the water-bath incubation of titrations or tests to which the cells have been added, shake the racks sufficiently to keep the cells in suspension. Do not shake the racks so continuously or violently as to cause foaming of the liquid.

The time and temperature of fixation is 4 hours in the refrigerator at from 3° to 6° C. Fifteen minutes' incubation at 37° C. is allowed for hemolysis. The temperature of the refrigerator or of the water bath in which tests are placed during the periods allowed for fixation or for hemolysis should not vary more than 1° above or below the temperature specified.

Record the hemolysis obtained in the different tubes of tests or titrations, and all necessary

data concerning them, directly on the cards or forms designed for each. Readings are made by comparison with color standards.

(a) *Suspension of Sheep Red Blood Cells*—To ascertain if the 5 per cent suspension of sheep cells is of approximately standard density, dilute a 0.5 cc quantity to 200 cc. with salt solution in a volumetric flask and determine its turbidity in a candle turbidimeter. If the turbidity lies between 220 and 230, consider the suspension to be satisfactory. Otherwise, make the necessary adjustments and determine that the

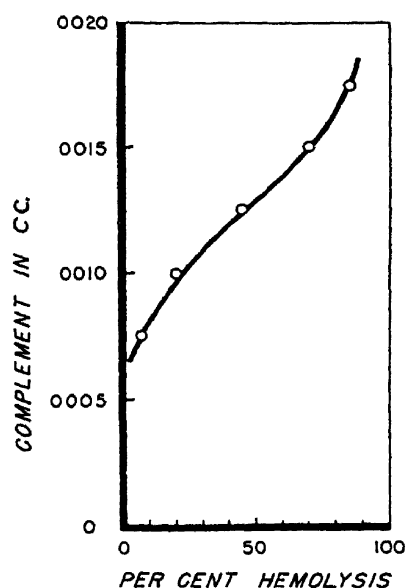


Fig. 1—Complement titration.

turbidity of the adjusted suspension is satisfactory before use.

(b) *Antisheep Amboceptor*—Amboceptor that has any appreciable agglutinating effect should not be used. To determine the agglutinating properties, add 0.1 cc. of different dilutions of the serum and 0.3 cc. of salt solution to tubes containing 0.1 cc. of a 5-per-cent suspension of sheep cells, and incubate for 30 minutes at 37° C. If no agglutination is evident at that time, make a second reading after the test has stood overnight in the cold room. Perform these tests with the cells of each sheep used. Discard any serum that causes agglutination in the dilution that proves optimum for use in the tests.

To determine the optimum quantity of amboceptor for use in the test, titrate complement as indicated in Table VIII, using a 5-per-cent suspension of cells sensitized with equal quantities of varying dilutions of the amboceptor outside the agglutinative range. Perform these titra-

tions with the cells from each sheep used. On cross-section paper, plot the degrees of hemolysis observed against the quantities of complement tested in each titration and fit a smooth curve to the points by inspection as illustrated in Fig. 1. Read from the curves the amounts of complement required for 50-per-cent hemolysis in the different titrations and plot them against the quantities of amboceptor used as indicated in Fig. 2 which records the results obtained with cells from 3 different sheep in titrations of 3

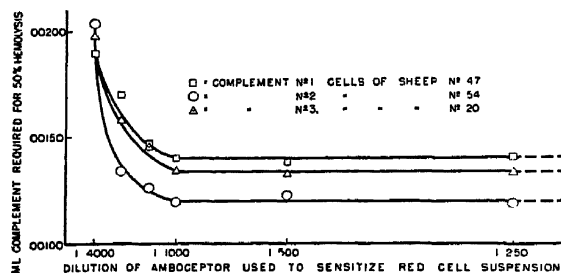


Fig. 2—Standardization of amboceptor.

pools of complement. Select as standard for use in tests the dilution of amboceptor that contains an amount beyond which further increase fails to diminish appreciably the quantity of complement required for 50-per-cent hemolysis. For example, of the dilutions used in the titrations of Fig. 2, the 1:1000 dilution would be taken as optimum.

In titrations of complement with cells sensitized with the standard dilution of amboceptor, the relations of other degrees of partial hemolysis to that of 50 per cent should not differ appreciably from those indicated by the conversion factors derived from titrations of complement alone, *i. e.*, without preliminary incubation and in the absence of serum and antigen. (See interpolation or conversion factors corresponding to a  $1/n$  value of 0.156, Table I, *Cyclopedia of Medicine, Surgery and Specialties*, vol. VII, p. 581.)

(c) *Complement*—To prevent the inclusion in the pooled complement of guinea-pig sera that are deficient or too potent in hemolytic activity, that contain excessive amounts of natural antisheep amboceptor, or that show, to a marked degree, the property of combining with antigen when no immune serum\* is present, the sera of the individual animals are subjected to preliminary tests on the day the guinea-pigs are bled, *i. e.*, the day before the serum is to be used for

\* Immune serum is used in a broad sense to mean all sera reacting specifically with antigen.

TABLE IX  
TEST OF INDIVIDUAL GUINEA-PIG SERUM FOR  
HEMOLYTIC ACTIVITY

Tube No.	Guinea-pig Serum (1:10)	Salt Solution	Sensitized Cells	Period for Hemolysis
1	cc 0.04	cc 0.26	cc. 0.2	15 minutes in the water bath at 37° C
2	0.01	0.29	0.2	

complement. Those found satisfactory for use are pooled and stored overnight in the refrigerator in a container packed in ice. The testing of individual sera for nonspecific fixability with antigen is of special importance, as indicated in practice for many years. This is particularly true when only a few guinea-pigs are bled; the presence in the complement of 1 serum possessing this property may result in a degree of nonspecific fixation that would affect the determination of the specific reaction.

*Preliminary Test of Hemolytic Activity*—Test each guinea-pig serum for hemolytic activity as indicated in Table IX.

Record the hemolysis with each amount of serum. Include in the pooled complement only the guinea-pig sera that give 95-100 per cent hemolysis in the larger amount tested. The test with the smaller amount serves in rare instances as a guard against including in the pooled complement too large a proportion of guinea-pig sera of unusually marked hemolytic activity.

*Test for Natural Antisheep Amboceptor*—Test each guinea-pig serum for natural anti-sheep amboceptor, including with each group of tests a control of the cells-suspension, as indicated in Table X.

Centrifugalize each tube to deposit the cells, and record the degree of hemolysis in each.

TABLE X  
TEST OF INDIVIDUAL GUINEA-PIG SERUM FOR  
NATURAL ANTISHEEP AMBOCEPTOR

Tube No.	Guinea-pig Serum (1:10)	Sheep Cells (5 Per Cent)	Salt Solution	Period for Hemolysis
1	cc 0.1	cc. 0.1	cc. 0.3	15 minutes in the water bath at 37° C.
2	None	0.1	0.4	

TABLE XI  
TEST FOR INDIVIDUAL GUINEA-PIG SERUM FOR NONSPECIFIC FIXABILITY

Tube No.	Antigen (dilution in use)	Guinea-Pig Serum (1 10)	Salt Solution	Fixation*	Sensitized Cells	Period for Hemolysis
1	cc 0.2	cc. 0.05	cc. 0.05	2 hrs. at from 3°-6° C	cc 0.2	10 minutes at 37° C.

\* In the complement-fixation tests for syphilis, the period for fixation is 4 hours at from 3° to 6° C, but in these preliminary tests the complement and antigen are exposed for only 2 hours at from 3° to 6° C, it having been found that guinea-pig sera which are markedly affected by exposure with the antigen for 4 hours are usually perceptibly affected in the shorter period. Also, as a result of experience, only the dilution found optimum for use with weakly reacting syphilitic serum need be used. A sample of each serum is tested also with fixation for ½ hour at 37° C, since, as explained under performing the test, certain supplementary tests with cholesterolized antigen are fixed at 37° C.

The hemolysis is due to natural antisheep amboceptor in the guinea-pig serum, provided the cells-control shows no hemolysis.

Include in the pooled complement only guinea-pig sera containing no more than a very slight amount of natural amboceptor according to this test.

*Test for Nonspecific Fixability*—Test each guinea-pig serum for nonspecific fixability as indicated in Table XI

Record the time required for complete hemolysis with each guinea-pig serum. If hemolysis is not complete at the end of 10 minutes, record the degree of hemolysis observed.

Include in the pooled complement only the sera with which 95-100-per-cent hemolysis occurs in 10 minutes or less.

*Titration of Pooled Complement*—On the day the complement is to be used, dilute 2 samples of the pooled serum, not less than 0.5 cc., 1:40, and titrate the hemolytic activity as shown in Table VIII.

In the complement titration, use sensitized cells prepared from portions of the 5-per-cent sheep-cell suspension and the standard dilution of amboceptor prepared for the day's work.

Prepare the sensitized cells required for complement-fixation tests from the diluted amboceptor remaining, not more than 10 or 15 minutes before it is time to add them to the first set of tests.

Record the degree of hemolysis in each tube.

On cross-section paper, plot the degrees of hemolysis observed against the amounts of complement tested (cubic centimeters of undiluted guinea-pig serum) and, by inspection, fit a smooth curve to these points. (See Fig. 1.) Determine from the curve the amount of complement that gives 50-per-cent hemolysis. This

should usually range from about 0.0013 to 0.0017 cc.

The results of tests may be less accurate when the quantity of complement giving 50-per-cent hemolysis appreciably exceeds these limits. When it is small, deterioration may be marked in tests incubated at 37° C, for example, in the preliminary complement-fixation tests for syphilis, and numerous reactions that are not significant may occur, necessitating either repetition of the tests or the examination of an undue number of specimens in the quantitative procedure. When the amount is unusually large, on the other hand, there may be danger of missing reactions of low degree because of the activating effect of patient's serum upon such complement. When pools of greater or of less than average activity, therefore, are used, it is the practice to adjust the quantity of complement giving 50-per-cent hemolysis before using it as a basis for preparing the dilutions of complement to be used in tests. Experience indicates that the amount of complement giving 50-per-cent hemolysis in titrations incubated for 15 minutes at 37° C. after the addition of sensitized cells, may be reduced by 5 per cent, when it is only slightly greater than 0.0017 cc., or by 10 per cent when it approaches 0.002 cc. When the amount exceeds 0.002 cc., the complement is discarded and a fresh pool obtained. On the other hand, when the quantity required for 50-per-cent hemolysis is as small as 0.0012 cc., it is increased by 3 per cent, or if as little as 0.001 cc., by 5 per cent. Complement more active than this has not been encountered.

The quantitative test, since the result is expressed as a ratio, is not greatly affected by these variations in complement activity. How-

TABLE XII  
TEST FOR ACCURACY OF COMPLEMENT DILUTION

Tube No.	Amount of Complement in 0.1 cc.	Amount of Dilution Used	Salt Solution	Sensitized Cells	Period for Hemolysis
	units	cc.	cc.	cc	
1	6	0.02	0.28	0.2	15 minutes in the water bath at 37° C.
2	3	0.04	0.26	0.2	
3	2	0.06	0.24	0.2	
4	1	0.12	0.18	0.2	

ever, the ratio Tables V-VII\*, that give the titers of reactions occurring with different amounts of complement, are based on determinations made with complement of average activity and might require a small correction to allow for changes in slope of the hemolytic curves that would be obtained with complement of definitely greater or less than average activity.

The amount of complement designated as a unit for use in any complement-fixation test should correspond approximately to the amount that would give 50-per-cent hemolysis under the conditions of the test. The titers of sera in different tests are then comparable, since they represent corresponding changes in the unit of complement. The unit amount need not, and in fact cannot, be determined exactly, because the effect of the time and temperature of fixation upon the hemolytic activity of complement may vary with every serum tested. It is important, however, that the different dilutions of complement used in tests be exact multiples of the amount taken as 1 unit.

Because fixation for 4 hours at from 3° to 6° C. has little or no effect upon the hemolytic activity of complement, the amount of complement required for 50-per-cent hemolysis in the titration just described can be taken as 1 unit for use in the complement-fixation test for syphilis. In the supplementary tests that require fixation for ½ hour at 37° C. and are done in certain instances as mentioned in the footnote of Table III,† a larger amount is necessary because of the greater deterioration of complement at this temperature. In the authors' experience, an amount 1.3 times that required for 50-per-cent hemolysis approximates satisfactorily the unit activity of complement under the

conditions of these tests. This amount may be considered as 1 unit in calculating the amounts of complement to be included in the different dilutions prepared or 0.13 cc. instead of 0.1 cc. of the usual dilutions of complement may be employed.

Multiply the cubic centimeters of complement representing 1 unit by 12 to determine the amount of guinea-pig serum to make a dilution containing 12 units in 0.1 cc., and calculate the amount of physiological salt solution required to dilute to that volume by subtracting the product from 0.1 cc. Prepare a mixture in this proportion sufficient for the day's tests and for the preparation of further complement dilutions needed.

After 5 or 10 minutes, prepare additional dilutions to contain 6, 3, 2, and 1 unit by adding to 1 part of the dilution containing 12 units 1, 3, 5, and 11 parts, respectively, of salt solution.

Check the dilutions, as indicated in Table XII. If the dilutions have been correctly prepared, each test of a given set of dilutions will contain the same amount of complement and should, therefore, give the same result. The degree of reaction may vary on different days between 70-per-cent and 85-per-cent hemolysis but the results on a given day should not differ by more than 10-per-cent hemolysis. If greater variation occurs, repeat the tests and, if there is evidence of error in dilution, prepare fresh dilutions and check them in the manner just described. When additional dilutions are needed, prepare and check them in a similar way.

(d) *Antigen*—Extracts of the type used have proved constant in antigenic activity over a period of years and amounts as large as desirable may be prepared at 1 time. Antigen is titrated before use for lytic and anticomplementary properties, and carefully standardized to determine the maximally reactive dose.

Dilute the cholesterolized tissue-extract antigen as follows: Place the required amount of

\* *Cyclopedia of Medicine, Surgery and Specialties*, Vol. VII, pp. 587-589.

† *Ibid.* Vol. VII, p. 585.

TABLE XIII  
TITRATION OF HEMOLYTIC PROPERTIES OF ANTIGEN

Tube No	Antigen	Complement (3 units)	Sheep Cells (5 per cent)	Salt Solution	Period for Hemolysis
1	cc. 0.4	cc 0.1	cc. 0.1	cc. 0.0	15 minutes in the water bath at 37° C
2	0.2	0.1	0.1	0.1	
3	0.1	0.1	0.1	0.2	
4	None	0.1	0.1	0.3	
5	None	None	0.1	0.4	

TABLE XIV  
DETERMINATION OF MAXIMALLY REACTIVE DOSE OF ANTIGEN

Syphilitic Serum Diluted in Normal Serum† 0.05 cc	Serum Controls			Tests with 0.1 cc Antigen Diluted in Salt Solution*											
				1 200	1 100	1 67	1 67	1 50	1 33	1 50	1 33	1 25	1 33	1 25	1 20
				Units of Complement in 0.1 cc.											
				3			6			9			12		
Undiluted . . .	x	x	x												
1:10 . . .										x	x	x	x	x	x
1:12.5 . . .							x	x	x	x	x	x	x	x	x
1:16.7 . . .				x	x	x	x	x	x	x	x	x	x	x	x
1:25 . . .				x	x	x	x	x	x	x	x	x			
1:50 . . .				x	x	x	x	x	x						

x = Tests made with each quantity of serum; fixation is for 4 hours at from 3° to 6° C.; after the addition of 0.2 cc. sensitized cells to each tube, 15 minutes in the water bath at 37° C are allowed for hemolysis

\* Each portion of cholesterolized antigen is tested in this way: Different dilutions in saline are used until the optimum (maximally reacting) dilution is found for each case. For an antigen with which 0.4 per cent cholesterol gives optimum sensitization, the dilutions of antigen indicated are usually satisfactory, whereas for one with which 0.2 or 0.6 per cent cholesterol would be optimum, lower or higher dilutions, respectively, would need to be substituted in the tests with each of the different quantities of complement

† Filtered pools of strongly reacting syphilitic serum are diluted in pooled, filtered, normal serum, each dilution being made separately from the undiluted syphilitic serum. The range of activity of the serum determines the dilutions to be used. For serum having a titer of approximately 100 with the standard antigen (See: DETERMINATION OF TITERS ABOVE 10) the dilutions indicated in the table are usually satisfactory but higher or lower dilutions may be used as necessary.

salt solution in 1 beaker and pipette the antigen to the bottom of another, then add the salt solution to the antigen as rapidly as possible and mix thoroughly by pouring from 1 beaker to the other several times.

**Titration of Hemolytic Properties**—Antigens are occasionally hemolytic in low dilutions. To detect this property, test alcoholic extracts in a 1:10 dilution, since a no more concentrated dilution would be used in any case. Perform the titrations as illustrated in Table XIII.

Centrifugalize the tubes to deposit the cells, and record the degree of hemolysis in each.

If there is no hemolysis in the control tubes 4 and 5, but marked hemolysis in tubes 1 to 3

containing antigen, the extract is unsatisfactory for use in quantitative tests.

**Determination of Anticomplementary Properties and of Maximally Reactive Dose**—Kent<sup>23</sup> has shown that there is an optimum ratio, cholesterol to extract, which exhibits maximum antigenic activity in complement-fixation tests for syphilis; also that cholesterol and extract in optimum ratio exhibit the same maximum activity whether extract is diluted in 1, 2, or 3 parts of alcohol before cholesterolization. In order to determine this ratio, extract must be tested in concentrations such that the optimum amount of cholesterol will fall within the range of the quantities that are soluble in the extract.

TABLE XV

UNITS OF COMPLEMENT REQUIRED FOR 50-PER-CENT HEMOLYSIS AS INDICATED BY THE DEGREES OF HEMOLYSIS OBTAINED IN TESTS WITH DIFFERENT AMOUNTS OF COMPLEMENT

Reagents Present	Units of Complement	Per Cent Hemolysis																	
		5	10	15	20	25	30	35	40	45	50	55	60	65	70	75	80	85	90
Test for syphilis—incubation for 4 hours at from 3° to 6° C, 15 minutes for hemolysis																			
Complement alone or with antigen	1	1.61	1.45	1.33	1.27	1.20	1.15	1.12	1.07	1.04	1.0	0.97	0.93	0.91	0.87	0.84	0.80	0.76	0.69
	2	3.22	2.90	2.67	2.53	2.41	2.30	2.25	2.15	2.08	2.0	1.94	1.87	1.82	1.74	1.68	1.60	1.52	1.39
With serum or with serum and antigen	1	1.78	1.54	1.39	1.32	1.23	1.19	1.12	1.09	1.04	1.0	0.96	0.93	0.88	0.85	0.81	0.76	0.71	0.65
	2	3.51	3.06	2.81	2.63	2.49	2.37	2.26	2.16	2.07	2.0	1.92	1.84	1.76	1.69	1.60	1.52	1.42	1.29
	3	5.02	4.45	4.12	3.88	3.69	3.52	3.37	3.24	3.10	3.0	2.86	2.75	2.64	2.52	2.40	2.26	2.12	1.92
With serum and antigen	6	9.05	8.25	7.75	7.40	7.20	6.80	6.65	6.35	6.20	6.0	5.76	5.59	5.39	5.16	4.93	4.65	4.37	3.98
	9	12.2	11.5	11.0	10.6	10.2	10.0	9.7	9.5	9.2	9.0	8.8	8.5	8.2	7.9	7.6	7.3	6.8	6.2
	12	15.0	14.4	14.0	13.5	13.3	13.0	12.7	12.5	12.2	12.0	11.7	11.5	11.2	10.8	10.5	10.1	9.5	8.8

Personal experience has shown that the antigenic activity of different extracts prepared in the manner described in the *Cyclopedia of Medicine, Surgery and Specialties*, vol. VII, p. 587, 1939, is quite similar. The optimum ratio of cholesterol to extract can usually be determined, therefore, by testing several portions of a single dilution of extract in alcohol, *e. g.*, 1 part of extract diluted with 2 parts of absolute alcohol, each containing a different amount of cholesterol varying from 0.2 to 0.6 per cent. Should an extract of unusual activity be encountered, it would be necessary to test other dilutions in alcohol or other amounts of cholesterol.

Dilute the several portions of cholesterolized antigen in saline and test in 0.1 cc amounts with varying quantities of strongly reacting syphilitic serum and 3, 6, 9, and 12 units of complement, as shown in Table XIV. Include tests of the anticomplementary properties of the different dilutions of the antigen, using 0.1 cc. amounts in the presence of 1 and 2 units of complement; and controls of 1 and 2 units of complement alone. When the sensitized cells are added to the tests, include also a control of sensitized cells to which salt solution alone is added. The controls of a given reagent need be included only in the first and last sets of tests made.

Record the degree of hemolysis obtained in each tube of the test. The control of sensitized cells should show no hemolysis; comparison of the reaction in the complement control with

that in the antigen controls affords a measure of the anticomplementary activity of the antigen. An antigen that has more than slight anticomplementary action in any of the dilutions tested is unsatisfactory for use in the quantitative test.

Evaluate the reactions in the different tubes of the test in terms of the number of units of complement required for 50 per cent hemolysis by reference to Table XV, which gives these values for the different degrees of hemolysis that may occur with each of the quantities of complement tested.\*

The selection of the optimum adjustment of cholesterol to extract is facilitated by indicating the results of the tests graphically. When the number of units of complement required for 50 per cent hemolysis are plotted against the quantities of serum tested with each portion of cholesterolized extract, a linear relation should obtain between serum and complement in those tests in which maximally reactive doses of antigen are present. This linear relationship should hold throughout the range of complement quantities used in the quantitative test, *i. e.*, with 3 to 12 units.

In the example given in Fig. 3 it is evident that the optimum amount of cholesterol is 0.4

\* These values correspond with those recorded in the rows opposite 50-per-cent hemolysis in the ratio charts, tables V, VI and VII, *Cyclopedia of Medicine, Surgery and Specialties*, Vol. VII, pp. 587-589, and include also values for reactions occurring with 1 and 2 units of complement.

per cent. With further addition of cholesterol, diminished serum reactions are observed, and smaller amounts are definitely less active. In similar tests of saline dilutions of portions of this antigen diluted with 1 or with 3 parts of alcohol, the optimum amounts of cholesterol are found to be 0.6 and 0.3 per cent, respectively. With undiluted tissue extract the optimum amount of cholesterol cannot, in this case, be

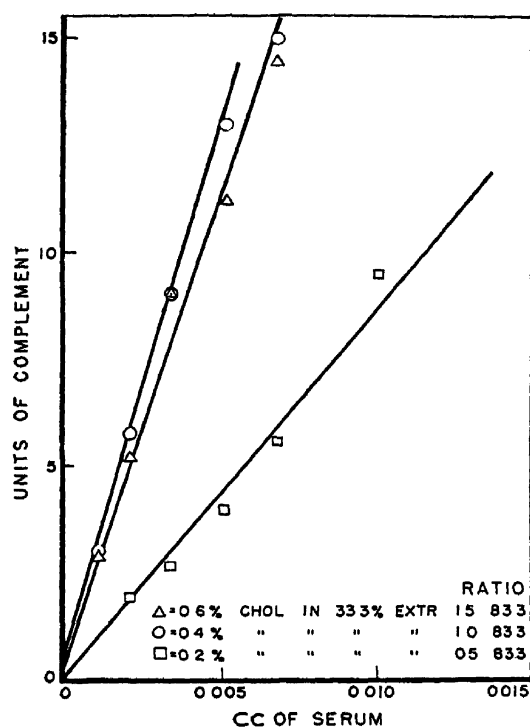


Fig. 3—Effect on antigenic activity of varying the ratio, cholesterol tissue extract. (J Immunol Reprinted by permission of Williams and Wilkins Co.)

determined due to the relative insolubility of cholesterol. In each case, the cholesterol-antigen ratio is 1:83.3.

When the optimum cholesterol-antigen ratio has been determined, a suitably cholesterolized portion of the antigen is studied further to determine the optimum amounts for use in tests with 3, 6, and 12 units of complement and sera of varying degrees of activity. Since prozone effects are observed, it is necessary to use in the quantitative test for syphilis a different amount of antigen with each of the 3 doses of complement—3, 6, and 12 units—in order to approximate the conditions for maximum reaction with sera of low, moderate, and marked activity within the range of titers up to 10. The range of antigen quantities used in standardizing antigen, and the number of determinations

made must be sufficient to indicate clearly in each case that both larger and smaller quantities of antigen are less active than the amount selected as the maximally reactive dose.

Experience indicates that the doses of antigen optimum for use in supplementary tests fixed for  $\frac{1}{2}$  hour in the water bath at  $37^{\circ}\text{C}$ , as well as the conversion factors derived from titrations at this temperature (see below) are the same as for those fixed for 4 hours at from  $3^{\circ}$  to  $6^{\circ}\text{C}$ . A brief check to determine this should be made, however, in each instance.

Select in the same manner as for serum, the dilutions of antigen that are optimum for use in tests of spinal fluids. In the writers' experience thus far somewhat higher dilutions of antigen than are used with serum appear to be optimum for use with spinal fluids. For example, the present antigen which is diluted 1:100, 1:50, and 1:25 for use in the test of serum with 3, 6, and 12 units of complement, respectively, is diluted 1:200, 1:100, and 1:33, for use in tests of spinal fluids.

**Determination of Conversion Factors**—The conversion factors for use with the present antigen are given in Table I, *Cyclopedia of Medicine, Surgery and Specialties*, Vol VII, p. 581. New conversion factors need to be determined only if the effect of a new antigen upon the slope of the hemolytic curve differs from that of the standard antigen. Such an effect is indicated if plots of the reactions with the new antigen, based on the values given in Table XV—which were derived from experiments with the antigen at present in use—do not show a linear relationship between serum and complement. Failure of the linear relationship in these graphs, however, may be due to other causes; for example, to the use of dilutions of the antigen other than those that are maximally reactive, or possibly to some property peculiar to the antigen under investigation. When it is necessary to determine new conversion factors, for use with a new antigen, titrations with amounts of guinea-pig serum ranging from 0.04 to 0.001 cc. in a geometric progression based on 0.9 should be made under conditions requiring various amounts of complement for 50 per cent hemolysis, *viz.*, in the presence of appropriate quantities of reacting serum and of the dilutions of antigen that appear to be maximally reactive.

Prepare a 1:25 dilution of pooled complement in a French-square bottle of about 100 cc. capacity by mixing 4 cc. of undiluted complement with 6 cc. of physiological salt solution.

TABLE XVI  
DETERMINATION OF CONVERSION FACTORS

Per Cent Hemolysis 100 Y	Complement			Log $\frac{Y}{1 - Y}$	4 + Log V		Log X Log V for Each Per Cent Hemolysis Minus Log V for 50% Hemolysis	X 50% Units or Conversion Factors
	Observed Values in cc. = V	V Read from Curve	50% Units or Conversion Factors		Observed	Read from Straight Line		
5	0.00075	0 00068	0.52	-1 279	0 8751	0.857	0.752	0 56
7				-1.173				
10		0 00079	0.61	-0.954		0.919	0 814	0.65
20	0.001	0.00096	0 74	-0 602	1 0000	0 987	0 882	0 76
30		0 00109	0 84	-0.368		1.031	0 926	0 84
40		0 00120	0 92	-0 176		1 069	0 964	0.92
45	0 00125			-0.087	1.0969			
50		0.0013	1.0	0		1.105	0	1.0
60		0 00140	1.08	0 176		1 139	0.034	1.08
70	0 0015	0.00151	1 16	0 368	1.1761	1.177	0.072	1.18
80		0 00166	1.28	0.602		1.225	0.120	1.32
85				0.699				
90	0 00175	0 00190	1.46	0.954	1.2430	1.293	0.188	1.54

Mix by tilting and gently rotating the bottle. Remove one-tenth of the total volume, *i. e.*, 1 cc., to the first of a series of test tubes and replace with 1 cc. of salt solution. Mix gently and remove 1 cc. to the second tube in the series and replace with 1 cc. of salt solution as before. Repeat the process until 36 dilutions are prepared. If a larger amount than 1 cc. of each of the complement dilutions is required, the amount of the original 1:2.5 dilution may be increased proportionally, as long as the progression of 0.9 is maintained in making the dilutions.

Pipette the reagents in the following amounts: complement, 0.1 cc. of the required dilutions (for this purpose, use the upper tenth of a 0.2-cc pipette, a separate pipette for each dilution, and deliver to the bottom of each tube); reacting serum of known titer in appropriate dilutions, 0.05 cc.; antigen, 0.1 cc.; salt solution, 0.05 cc. After fixation, add 0.2 cc sensitized cells and complete the titrations in the usual way.

Plot the different percentages of hemolysis obtained against the amounts of complement tested. Fit a smooth curve by inspection to each titration. From those titrations in which the quantities of complement required for 50 per cent hemolysis correspond approximately to the amounts representing 3, 6, and 12 units as used in quantitative tests, determine the 50 per cent unit values, *i. e.*, the conversion

factors for different percentages of hemolysis from 5 to 90 at intervals of 5 per cent. These conversion factors may be determined (1) by plotting the amounts of complement (in cubic

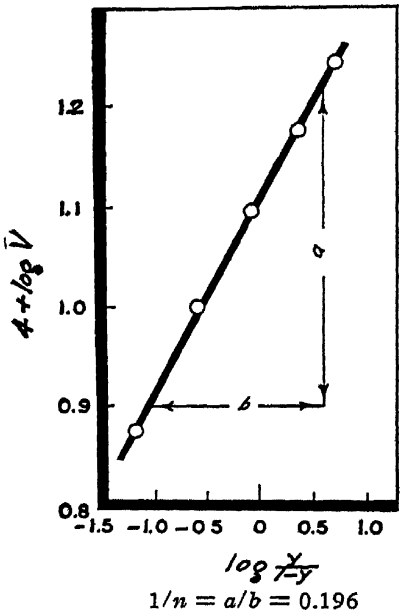


Fig. 4—Logarithmic plot of a complement titration

centimeters) against the degrees of hemolysis obtained in the titrations, fitting, by inspection, a smooth curve to the experimental points in each titration as in the example given in Fig. 1, and dividing the amount of complement indi-



TABLE XVII  
RESULTS OF A TYPICAL TEST TO DETERMINE TITER GREATER THAN 10

Syphilitic Serum		Serum Controls			Tests with Antigen W34, Diluted 1 3 with Alcohol and Containing 0 4% Cholesterol, Diluted in Saline*								Evaluation of the Reactions in Terms of Complement Units Required for 50% Hemolysis	
Dilution in Normal Serum, 0 05 cc	Equiva- lent Amount of Serum				1 200	1 100	1 67	1 50	1 50	1 33	1 33	1 25		
		Percentage of Hemolysis Observed with Units of Complement†										Serum Alone (IS)	Serum + Antigen (IS + A)	
		1	1	2	3		6		9		12			
Undiluted	0 05	40	40	95									1.09	
Diluted														
1:2 5 .	0.02						0	0	25	15	90	75		11 0
1 5	0 01				15	0	45	45	95	100	100	100		6.2
1:10	0.005				40	35	100	100	100	100	100	100		3 4
1.25 ..	0.002				80	90	100	100	100	100	100	100		2.3

\* In the test to determine titers under 10, antigen is diluted 1:100, 1:50, and 1:25 for use with 3, 6, and 12 units of complement, respectively, because these dilutions elicit maximum reactions in the vast majority of cases with sera having titers within the range up to 10. In determining titers above 10, the use of an additional dose of complement, 9 units, and of 2 doses of antigen with each dose of complement, facilitates the determination of the maximum reaction with each quantity of serum tested.

† The percentages of hemolysis representing the maximum serum reactions are bold face

cated on the curve for a given degree of hemolysis by the amount for 50 per cent hemolysis, *i. e.*, by expressing in terms of 50 per cent units (column 4 of Table XVI); or (2) as was done in computing the conversion factors given in Table I, *Cyclopedia of Medicine, Surgery and Specialties*, Vol. VII, p. 581, by using the observed fact that if  $X$  is the amount of complement required for a given degree of hemolysis,  $Y$ , then the experimental points ( $\log X, \log \frac{Y}{1-Y}$ ) fall approximately on a straight line, *i. e.*,  $\log X = \log K + 1/n \log \frac{Y}{1-Y}$  where  $K$  is the value of  $X$  for  $Y = 0.5$  and  $1/n$  is a parametric constant. This constant is equal to the slope of the line, which appears to vary inversely with  $K$ , the amount of complement required for 50 per cent hemolysis. An evaluation of  $1/n$  may be obtained directly by plotting  $\log V$ , where  $V$  is the corresponding volume of complement used experimentally, against the logarithm of  $\frac{Y}{1-Y}$  and determining the slope of a fitted straight line as illustrated in Fig. 4 where  $1/n = 0.196$ . The conversion factors may be calculated by reading from the fitted line the values for  $\log V$  for different values of  $\frac{Y}{1-Y}$  and subtracting the value of  $\log V$  where  $Y = 0.5$  (50 per cent hemolysis), which will give the corresponding values of  $\log X$ . The corresponding antilogarithms will

be the required conversion factors. Table XVI illustrates the calculations for determining conversion factors by both methods. Fig. 4 is a logarithmic plot of the same complement titration illustrated in Fig. 1. Conversion factors as determined by the 2 methods are essentially the same, but significant deviations from the usual reaction, which may occur in individual titrations, are more readily detected by the second method. Fig. 4 also illustrates the method of determining the slope,  $1/n$ . For further details, the reader is referred to other publications.<sup>79, 80</sup>

Perform titrations sufficient in number to establish accurately new conversion values for use with the new antigen. If reactions in tests with the new antigen when evaluated by the proper conversion factors do not indicate linear relationships between complement and serum, the antigen is unsatisfactory for use in quantitative tests.

A new antigen is compared with a previously standardized antigen in parallel quantitative tests of appropriate sera of varying degrees of activity. These should include specimens from persons with different forms or in different stages of syphilis, or under treatment, as well as some from persons with other infections, and from apparently healthy individuals.

**Quantitative Complement-fixation Test**  
—*Determination of Titers up to 10*—For the method of performing the test to determine

titers up to 10, the preparation of color standards and the method of reading, recording, and reporting results, see *Cyclopedia of Medicine, Surgery and Specialties*, Vol. VII, pp 586-590, and Tables III to VII.

All spinal fluids receive a complete quantitative complement-fixation test but as a technical control, a 1-tube test of each specimen is performed by a separate group of workers; 0.2 cc. of spinal fluid is used and the test is the same as the preliminary test of serum except that 4 hours in the refrigerator at from 3° to 6° C. are allowed for fixation.

#### *Determination of Titers Greater Than 10—*

The titer of a serum in the quantitative test is expressed in terms of the maximum reaction obtainable with 0.05 cc. of the serum. In order to determine the end-point titer of highly active sera from patients, smaller amounts of serum are tested. Under these conditions, the titer cannot be read directly from the ratio tables but must be computed from data which determine the linear relationship between complement and serum.<sup>79, 80</sup> The computation is made by use of the formula,

$$\frac{D[(IS + A) - C'] + C'}{(IS)}$$

in which  $(IS + A)$  represents the units of complement required for 50-per-cent hemolysis in the presence of diluted serum and the maximally reactive dose of antigen,  $(IS)$ , the units of complement required for 50-per-cent hemolysis in the presence of undiluted serum,  $D$ , the relative serum dilution, *i. e.*, 0.05 cc. divided by the cubic centimeters of serum used in the tests with antigen; and  $C'$  the value obtained by plotting the units of complement required for 50-per-cent hemolysis in the presence of antigen and different quantities of serum directly against the quantities of serum used, and extending the straight line thus obtained until it intersects the complement axis; the intercept value being  $C'$ .

The method of testing is similar to that outlined in Table XIV. Use antigen in the maximally reactive doses with 4 amounts of complement—3, 6, 9, and 12 units—and vary the quantity of serum so that the maximum reaction of each amount, with antigen, is represented by a degree of partial hemolysis with at least 1 of the 4 quantities of complement tested. Evaluate the reaction of each quantity of serum, in the test with antigen as well as in the serum control, in terms of the units of complement required for 50-per-cent hemolysis,

by reference to Table XV, which gives these values for the different degrees of reaction that may occur with each of the quantities of complement used. Table XVII illustrates the type of result that is obtained

Plot the maximum reaction obtained with each amount of serum against the quantities of serum tested. If maximum reactions have been obtained with the different quantities of serum, the points plotted will fall approximately in a

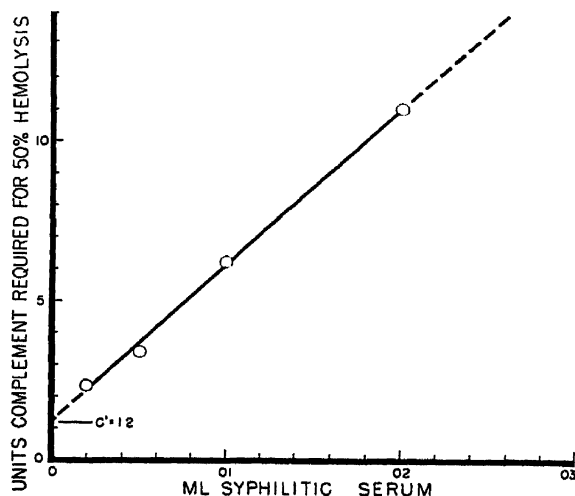


Fig. 5—Determination of  $C'$  from linear relationship observed between complement and serum with maximally reactive dose of antigen.

straight line. If maximum reactions have not been obtained, repeat the test using, if necessary, other amounts of serum. Extend the straight line until it intersects the complement axis and read in units of complement, at this point, the value of  $C'$ , as indicated in Fig. 5.

To determine the titer, substitute in the formula the value of the maximum reaction with any dilution of serum as indicated at any point on the straight line, together with the values determined for  $(IS)$  and  $C'$ . As shown in Table XVIII, the titer computed in this way—which is 24 in the example given—will equal or approximate closely the average of the titers derived by substituting in the formula the values of the maximum reactions that were determined experimentally.

Titers as high as 2000 have now been determined. In routine practice reports differentiate only those sera with titers up to 10, *i. e.*, the range of reactivity that is of especial importance as an aid in diagnosis and treatment. Titers above 10 are helpful in following the

TABLE XVIII  
CALCULATION OF TITER\*

Units of Complement Required for 50% Hemolysis with		Titer of Serum Calculated from the Formula $\frac{D[(IS + A) - C'] + C'}{IS}$
Undiluted serum alone (IS).	1.09	
Diluted serum + antigen (IS+A)		
1:2 .	13.5†	$\frac{2(13.5 - 1.2) + 1.2}{1.09} = 24.$
1.5	6.1†	$\frac{5(6.1 - 1.2) + 1.2}{1.09} = 24$
1:2.5	11.0	$\frac{2.5(11 - 1.2) + 1.2}{1.09} = 24.$
1.5	6.2	$\frac{5(6.2 - 1.2) + 1.2}{1.09} = 24.$
1:10	3.4	$\frac{10(3.4 - 1.2) + 1.2}{1.09} = 21.$
1.25	2.3	$\frac{25(2.3 - 1.2) + 1.2}{1.09} = 26.$
		Average = 24

\* Titers are recorded in 2 significant figures

† Values taken from fitted straight line (Fig. 5), others are experimental, as given in Table XVII.

effect of treatment but are determined only in special instances. Experience thus far indicates that the accuracy of the methods of determining titers above and below 10 is approximately the same. Differences in titer obtained on successive days in 50 per cent of cases is 8 per cent or less; for example, a change in titer of not more than from 8 to 8.7, or *vice versa*, or in the case of specimens with high titers, of a difference between 80 and 87, which represents a corresponding discrepancy. In only 10 per cent of cases have differences of more than 25 per cent been observed, *i. e.*, differences greater than those between 7 and 9, 70 and 90, or 700 and 900, all 3 of which represent the same relative divergencies. When a fairly marked discrepancy has occurred in successive tests, the examination of an additional specimen will almost invariably establish the correctness of a titer. Further work is in progress to determine so far as possible the causes of these variations so as to reduce to a minimum the necessity for repeated tests and to establish the accuracy of the titer within narrower limits. Obviously, variations such as those described are not great enough to impair the value of the test as an aid in diagnosis or in following treatment.

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## MEDICINE

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### AVIATION MEDICINE

*By* LOUIS HOPEWELL BAUER, A.B., M.D.

**Vision**—Owing to the fact that practically all commercial flying is done in cabin ships, the disadvantages of corrected vision no longer are important so long as the pilot has a reasonable amount of uncorrected vision. Hence, while military pilots are still required to have normal vision without correction, commercial pilots are permitted to wear glasses if their glasses correct their vision to 20/20 and their uncorrected vision is not worse than 20/50. Private pilots are required to have at least 20/30 vision with correction but there are no limits on the uncorrected vision which is less important in sport flying.

**Color Blindness**—Although there have been numerous lay references about color-blind individuals being able to detect camouflage better than those who have normal color vision, there is absolutely no scientific basis for such statements. In the light of present knowledge, the necessity for flyers to have normal color vision remains important.

**Effects of Altitude—Heart**—Considerable new work has been accomplished in this subject and the most recent may be summarized as follows:

Armstrong<sup>1</sup> has said: "The effect of anoxia on the heart muscle is the same

as that for any other tissue and the heart will continue to function long after the respiratory centers have become paralyzed. The electrocardiographic changes from anoxia consist essentially in a lowering or inversion of the T-waves, a depression of the R-T-interval, and sometimes a deformity of the QRS."

He states further: "The question of how much heart disease should be allowed in pilots and passengers has never been definitely settled but the final answer will depend, among other things, on the amount of anoxia to which they will be subjected in their flying."

Kountz and Gruber<sup>2</sup> have shown that anoxia produces characteristic changes in the electrocardiogram, the initial change observed by them being a decrease in the amplitude of the T-wave followed by inversion if the anoxia was progressive—the latter occurring usually at 30 per cent unsaturation of the arterial blood. Other workers have reported the same findings plus a depression of the R-T-segment. Graybiel<sup>3</sup> reported slight variations in the P-R-interval and QRS-complexes.

Benson<sup>4</sup> found that there were no changes in the electrocardiogram up to

30,000 feet if oxygen were administered.

The latest work on this subject has been by White.<sup>11</sup> Forty-five subjects were exposed to altitude flights without oxygen. Two series were studied. Twenty-five were exposed to 20,000 feet, one-half ascending to that level in 1 hour, the other half in 2 hours. The second group of 20 was taken to 15,000 feet and held there for 2 hours.

In the 20,000 feet group there was a progressive diminution of the height of the T-wave in all subjects in all 4 leads. This decrease in height began as low as 5000 feet. With the administration of oxygen, there was a restoration to normal height. In the 15,000 feet groups there were similar changes but a tendency to return to normal was noted. One case developed a shift of the pacemaker. As a rule, in the group that ascended more slowly the changes were lessened.

As a result, White<sup>5</sup> recommends the use of **oxygen** at 7500 feet as a precaution.

Graybiel<sup>3</sup> and his associates at the Harvard Fatigue Laboratory found that the effects of **benzedrine sulfate** on the cardiovascular system could be summarized as follows:

"1. The administration of 20 mg. of benzedrine intramuscularly causes a slight but well sustained increase in systolic blood-pressure, very slight increases in pulse rate and only minor changes in the electrocardiogram.

"2. When benzedrine is administered during exposure to low oxygen tensions, there is a slight increase in pulse rate. Benzedrine has a favorable action in preventing the fall in blood-pressure during anoxemia.

"3. The electrocardiographic alterations following the administration of benzedrine are slight. This drug tends

to prevent the lowering of the T-waves which may occur during exposure to low oxygen tensions."

In 1937, Bishop<sup>6</sup> made a study of the question "Is it safe for the heart patient to fly?" This paper was presented before the Aero Medical Association and received considerable discussion. The sum and substance was that there were 2 factors to be considered in the case of the cardiac, *i e.*, (1) the psychological factor associated with the apprehension of first flight, and (2) oxygen want associated with altitude. Apprehension causes acceleration of the heart rate and in the hypertensive and potential hypertensive, an increase in blood-pressure.

In the person accustomed to flying and who is philosophic about it, there is no more danger in flying than in going by auto or train—except for the effects of altitude, which can be relieved by the administration of oxygen.

Is flying a type of occupation that induces coronary disease? Smith, of the Mayo Clinic, found that of 93 cases of coronary sclerosis, 10.7 per cent were in doctors, 5.3 in bankers, 4.6 in lawyers, 4.6 in clergymen, 2.6 in farmers, and 2.6 in laborers; making the percentage 6.3 in mental workers and 2.6 in the physical workers.

Leedham<sup>7</sup> believes that flying with its tremendous responsibility with property, lives, schedules, and the mental strain plus irregular hours, places it in a class with the practice of medicine so far as wear and tear on the body is concerned; the degenerative hazards will be about equal.

**Barometric Pressure** — Armstrong<sup>1</sup> has called attention to the fact that the gases in the gastrointestinal tract will expand in direct proportion to the decrease of atmospheric pressure and notes that at 38,000 feet these gases have expanded 5 times their original volume

and at 52,000 feet 10 times their original volume. If the flyer ascends slowly, say at 200 to 300 feet per minute, there is a tendency to belch gas and pass flatus until distention no longer exists. If the ascent, however, is at a rate of 1000 feet or more per minute the gas tends to become pocketed and cramps occur which are severe and may persist even after return to sea-level.

The most dangerous effect of reduction of barometric pressure is considered to be the development of *aero-embolism* due to the formation of nitrogen bubbles in the blood which are given off just as in caisson disease from too rapid decompression. Armstrong, again, has written most fully on this subject. He reports that the nitrogen bubbles develop at any ascent in excess of 78 feet per minute. He reports it of no importance until an altitude of 30,000 feet is reached and definite symptoms develop above that level if the ascent exceeds 200 feet per minute. Bubbles of nitrogen appear in the spinal fluid even at 18,000 feet in animals. He describes the symptoms as pain in tissues such as bone, tendons, fascia, periosteum and nerve sheaths. Disorientation may occur. He warns of the danger of *aero-embolism* in an end-artery causing infarction. Edema of the lungs may result.

As a *preventive*, planes should not ascend above 30,000 feet and the rate of ascent should be slow, neither of which is practical in military aviation. Breathing pure *oxygen* has been recommended highly by Behneke. The breathing of 100 per cent oxygen should be started some time before leaving the ground. This method has been used extensively in Europe, but recently there has been an unofficial report that it has been given up by the Royal Air Force as not being satisfactory. *Recompression* with continued breathing of 100

per cent *oxygen* is the treatment for an actual attack.

Much work remains to be done on this subject and it is one of the most important problems in aviation medicine.

*Oxygen Equipment*—For many years satisfactory equipment for supplementary oxygen was sadly lacking. Various apparatuses were developed that failed to function at the extreme cold of high altitudes and they were discarded. The old so-called "pipe-stem" method was used. This was unsatisfactory for several reasons. It caused dryness of the mouth and throat; it gave inadequate help because the flyer also breathed through his nose and if it slipped out of his mouth, he could easily faint before he could find it and reinsert it. Any apparatus that is to be wholly satisfactory must be simple, effective, and require little attention for its use. Recently, 2 masks have been developed which are satisfactory, the first, the B.L.B. mask<sup>8</sup> and later that recommended by Barach.<sup>9</sup>

The altitude at which oxygen should be used is gradually being generally accepted as at lower and lower levels. First it was 15,000 feet, then 12,000, later 10,000, and recently 7500 feet has been recommended.

*Speed*—Planes are continuing to fly at increasing speeds and in dive-bombing the plane may reach a speed of 500 miles per hour at the time of pull-out. In pulls along the long axis of the body; the human being is accustomed to a pull of 1 G, *i e.*, the pull of gravity. Again quoting Armstrong,<sup>1</sup> as the pull increases up to 5 G's, there is first a sensation of heaviness, and movement of the muscles is difficult. At 5 G's muscular control is impossible. Unconsciousness develops above that.

The effects may be in part alleviated by the use of an *abdominal belt* to prevent pooling of the blood in the

splanchnic area. Test and bombing pilots also yell at the top of their lungs as they reach high speeds, which tends to keep some of the blood in the head.

It is understood that automatic controls of dive-bombing planes are being developed so that in case the pilot does become unconscious, as he often does after the pull-out, the plane will fly itself until he comes to.

Various workers also are conducting research with the electro-encephalogram in an effort to find surer methods of selection and to study further the effects

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## CARDIOVASCULAR SYSTEM

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### ARTERIAL HYPERTENSION

#### Rôle of Kidney in Pathogenesis—

The experiments of Goldblatt, showing that arterial hypertension may be produced in dogs by partial constriction of the renal arteries by means of silver clamps, have thrown new light on the rôle of the kidney in the etiology of arterial hypertension. In a discussion of the part played by the kidney in the pathogenesis of arterial hypertension, Dicker<sup>1</sup> presents the histories of 2 patients, one of whom after an intoxication of undetermined origin had cessation of renal excretory function without hypertension, and the other who, secondarily to scarlet fever, showed marked hypertension without, for a long time, any accompanying signs of renal excretory insufficiency.

CASE 1.—Gil. M., female, aged 30, was admitted to the hospital on Jan. 13, 1938, with almost total anuria, lumbar and polyarticular pains, severe headache and poor general condition. A week before, following an abortionist's manipulation, she had a temperature of 102° F. (38.9° C.) and generalized jaundice.

Since then, had violent pains in the region of the kidneys and scarcely urinated any more. In the clinical examination, the pertinent findings were A pale face and very dry lips; normal heart action; blood pressure was 112/55; pulse 80 and regular; the breathing was irregular, reminiscent of the Cheyne-Stokes type, but the lungs were normal; ocular fundi were normal. The clinical examination revealed nothing significant, but the analysis of blood and urine was diagnostic.

Analysis of blood showed: urea, 456 mg.; chlorine, 225 mg.; calcium, 7.96 mg.; uric acid, 23.9 mg.; and CO<sub>2</sub> combining power, 25.1 vol. per 100 cc. of plasma; red corpuscles, 1,460,000; white corpuscles, 6400; hemoglobin, 25 per cent. Urine analysis: Dilute and contained only 1090 mg. urea, and 40 mg. chlorides per 100 cc.

The tests for renal function showed significant impairment; Ambard,  $K = 1.630$  (4.3 per cent of normal); Van Slyke,  $C = 1.900$  (3.6 per cent of normal); Rehberg,  $F = 9.760$  cc. per minute.

The intradermal injection of a drop of histamine and of acetyl-choline gave rise to normal zones of erythema (35 cm.<sup>2</sup> and 21 cm.<sup>2</sup>), and the dermographic latency period was normal (5 seconds).

To sum up, the patient, from an undetermined toxic cause, showed an almost complete



abolition of renal secretion with enormous nitrogen retention, marked anemia, but no hypertension

Ten days after admission, the azotemia was still very high, the highest level of urea reached during this period was 527 mg. The output of urine gradually increased to well above 1000 cc. in 24 hours, but without any improvement in the concentration, which remained, on the whole, comparable to what it was at the beginning. Four days later, tests for renal function showed very slight improvement.

The striking thing is that, in spite of the intense and prolonged nitrogen retention, the arterial pressure showed no tendency to rise; it remained at 115/55. Correspondingly, the zones of erythema following the intradermal injection of a drop of histamine or of acetylcholine remained normal, and the period of dermographic latency remained at 5 seconds.

Slowly the patient's condition improved. About a month after her admission, N.P.N. was 30 mg., and Ca was 10.2 mg. per 100 cc. of plasma, but uric acid remained high, 11 mg. per 100 cc. The anemia slowly improved; red corpuscles, 2,880,000 per cm. Eventually, the urinary secretion also improved; about 2000 cc. in 24 hours, and the concentration was better. At this time renal function tests showed: Ambard,  $K = 0.140$  (50 per cent of normal); Van Slyke,  $C = 27.07$  (37 per cent of normal); Rehberg,  $F = 74$  cc.

In this condition the patient left the hospital at the end of 7 weeks. She has been seen periodically, and the improvement has continued, but extremely slowly. Altogether, 6 months were necessary to restore her health. At the present time, *i. e.*, after 12 months, the function of the kidneys has become completely normal. The arterial pressure, which did not vary during the whole course of the nephropathy, remains low, at about 120/55. The anemia has entirely disappeared.

CASE 2.—Pi A., female, aged 28, was admitted to the hospital on Dec. 21, 1937, for palpitation of the heart that occurred after the least effort. This condition, which dated back 2 years and began after an attack of scarlet fever, prevented the patient from doing work. A physician, consulted a year ago, is said to have found albuminuria in very slight quantities and prescribed an appropriate regimen with rest. Suddenly, 2 months before admission, during the night, there occurred an attack of suffocation and anxiety which lasted, according

to the patient's statement, several hours. This recurred, always in the night. For 2 months there was also frequent migraine, accompanied by black scotomas and noises in the ears.

The patient lay calmly in bed, showing neither cyanosis nor any trace of edema. The heart, on percussion, was slightly enlarged. On auscultation, a gallop rhythm and metallic second sound were heard. The pulse was tense, arterial pressure high, 220/142. The examination of the abdomen and of the nervous system revealed no abnormality. The ophthalmoscopic examination showed old scars of exudative retinitis and abnormally contracted arteries.

Analysis of the blood showed: urea, 25 mg., calcium, 10 mg., glucose, 98 mg.; uric acid, 3.8 mg.; cholesterol, 142 mg.; and  $\text{CO}_2$  combining power, 52 vol. per 100 cc. of plasma. Urine: no albumin, no sugar and microscopic examination negative. Renal function tests: Ambard,  $K = 0.0520$  (134 per cent of normal); van Slyke,  $C = 123$  per cent of normal; Rehberg,  $F = 165$  cc. per minute. Reactions of the peripheral vessels: dermographic latency period, 2 to 3 seconds; areas of erythema, to histamine, 21 cm<sup>2</sup>, and to acetylcholine, 13 cm<sup>2</sup>.

This condition remained without appreciable change during the whole period of her 6 weeks' stay in the hospital. Arterial pressure remained unchanged at a high level; signs of vascular spasm were always present, and renal function remained excellent. The patient was seen again 10 months later in a state of obvious physical distress. There was marked emaciation. On the body were seen purpuric spots and numerous ecchymoses. The heart beat was forcible and irregular. Arterial pressure was 235/162. There was no visible edema. The lungs were full of râles, due to stasis, and there were numerous transient crises of acute edema of the lungs. The urine contained minute traces of albumin; the microscopic examination showed numerous white corpuscles, some red corpuscles, and rarely, some casts.

The renal function tests were still within the limits of normal. The blood analysis, however, showed a slight increase of uric acid, 5.9 mg. per 100 cc.; whereas the N.P.N. remained about normal, 34 mg. per 100 cc. The blood count revealed a marked anemia, 2,100,000 red corpuscles. The alkali reserve was low, 38 vol.  $\text{CO}_2$  per 100 cc.

Investigations of the state of vasoconstriction of the peripheral vessels showed: Dermographic latency period, 2 to 3 seconds; areas of

splanchnic area. Test and bombing pilots also yell at the top of their lungs as they reach high speeds, which tends to keep some of the blood in the head.

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To sum up, the patient, from an undetermined toxic cause, showed an almost complete

any accompanying rise of arterial pressure, unless, as is frequently the case, the kidney is also the seat of vascular disease." The conclusion is: For the kidneys to be able to cause hypertension, their circulation must be restricted; and all the other renal and urinary manifestations are secondary, independent, and incapable of playing a part in the production and maintenance of the hypertension.

had evidence of advanced organic arterial damage; and in 3 cases in which data regarding the duration of the hypertension were available it had not existed for a long period. All the patients had relatively high diastolic blood-pressure compared with the systolic. In every case the kidney was contracted and atrophic, weighing less than 75 grams (less than half the normal weight); all had extensive chronic pye-

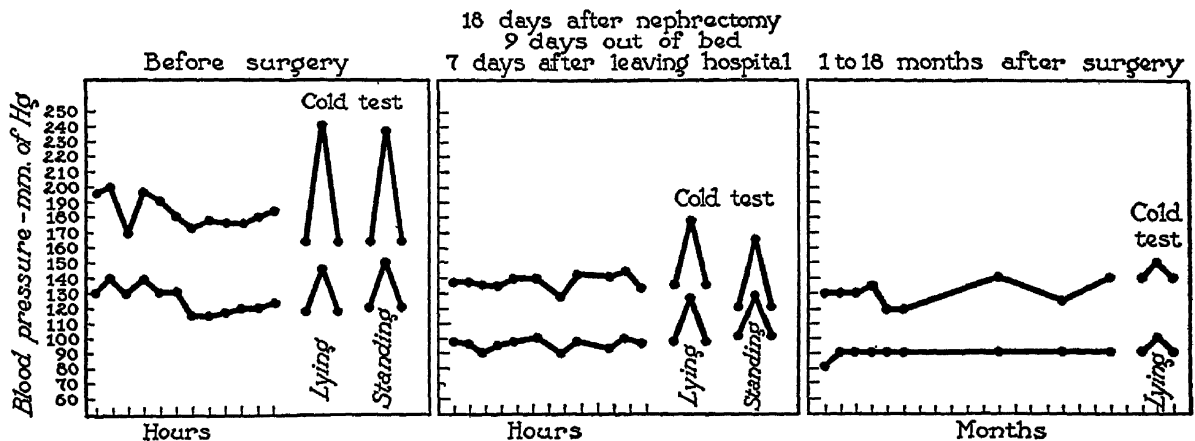


Fig 1—Hourly blood-pressures taken with patient at rest, reactions to cold pressor test and follow-up studies in Case 1 before and after nephrectomy. (Barker and Walters: J. A. M. A.)

**Hypertension and Chronic Atrophic Pyelonephritis** — Although in the majority of cases of essential hypertension there is no evidence of pyelonephritis, various investigators have felt that the association of these conditions is frequent enough to be more than incidental. In each of 5 cases of arterial hypertension associated with unilateral chronic atrophic pyelonephritis reported by Barker and Walters<sup>2</sup> the blood-pressure returned to normal after nephrectomy; and in 4 of them it has remained within normal limits for a number of months (insufficient time has elapsed to evaluate thoroughly the fifth case) (Fig. 1.). In each case pathologic studies revealed extensive atrophy and scarring of the diseased kidney with marked thickening of the walls of arteries in the scarred portions. None of the patients

lonephritis with destruction of renal parenchyma, with marked thickening of the arterial walls in the scarred regions. In a study of the vascular changes in pyelonephritis and their relation to hypertension, Weiss and Parker found that a mild degree of hyperplastic arteriolar sclerosis in both kidneys is usually associated with normal blood-pressure, a severe degree of hyperplastic arteriolar sclerosis in unilateral pyelonephritis may or may not be associated with hypertension, and a severe degree of hyperplastic arteriolar sclerosis in both kidneys is practically always associated with severe hypertension.

In the 5 cases reported by Barker and Walters the cause of the marked thickening of the renal arteries was not determined. In the regions in which the renal parenchyma was well preserved the ar-

TABLE I

BLOOD PRESSURE WHEN PATIENTS WERE FIRST OBSERVED AT THE CLINIC AND PATHOLOGIC CHANGES IN CASES OF UNILATERAL CHRONIC ATROPHIC PYELONEPHRITIS IN WHICH NEPHRECTOMY WAS PERFORMED

Case	Age, Yrs.; Sex	Blood Pressure, Mm. of Mercury	Weight of Kidney Gm	Renal Lesions and Percentage of Renal Parenchyma Involved by Scar Tissue	Thickening of Arterial Walls, Grade*
1	42, ♂	232/135	48	Nodular chronic pyelonephritis; 50%	3+
2	46, ♂	178/118	70	Nodular chronic pyelonephritis, large stone; 50%	3+
3	34, ♀	200/126	18	Diffuse chronic pyelonephritis, very little normal parenchyma	3+
4	52, ♀	186/110	52	Chronic nodular pyelonephritis, thickened parenchyma; 60%	4
5	7, ♀	210/ 66	9	Diffuse chronic pyelonephritis, many hyaline glomeruli	3
6	44, ♀	200/130	50	Granular chronic pyelonephritis, 60%	3+
7	43, ♀	170/112	30	Nodular chronic pyelonephritis, 60%	3+
8	57, ♂	184/112	50	Nodular chronic pyelonephritis; 30%	3+
9	47, ♀	170/100	70	Nodular chronic pyelonephritis, 40%	3+
10	39, ♀	250/140	60	Nodular chronic pyelonephritis, 50%	3+
11	36, ♀	220/130	20	Diffuse chronic pyelonephritis	3+
12	47, ♂	152/102	70	Nodular chronic pyelonephritis; 20%	3
13	37, ♀	160/ 88	70	Nodular chronic pyelonephritis, 10%	1+
14	48, ♀	162/ 88	48	Nodular chronic pyelonephritis, 50%	3+
15	49, ♀	155/ 90	60	Nodular chronic pyelonephritis, 47%	3+
16	26, ♀	125/ 90	42	Small hydronephrotic sac with diffuse chronic pyelonephritis	3
17	21, ♀	128/ 92	44	Nodular chronic pyelonephritis, 50%	3+
18	10, ♀	100/ 50	25	Nodular chronic pyelonephritis; 50%	3
19	39, ♀	130/ 90	68	Chronic pyelonephritis with pyonephrosis	3
20	50, ♂	110/ 74	52	Chronic pyelonephritis with pyonephrosis	3
21	41, ♂	124/ 86	70	Small hydronephrosis with a few scars	2
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\* Basis of 1 to 4.

teries appeared to be normal. The thickening was not confined to the arterioles; it was also seen in the interlobular and arcuate arteries. It was partly due to increased thickening of the muscular coat and partly to extensive hyperplasia of the intima. It may be the result of: (1) Arteritis which is part of the chronic inflammatory reaction in the renal parenchyma; (2) contraction by the scar tissue, and (3) more distal obstruction to the capillaries associated with the destruction of the renal parenchyma.

A review of a consecutive series of 57 cases, in which a diagnosis of chronic atrophic pyelonephritis was made by

urographic examination, revealed that 26 (45.6 per cent) had a blood-pressure greater than 145 systolic, 90 diastolic. In a series of 24 cases in which chronic atrophic pyelonephritis was diagnosed pathologically after nephrectomy, 15 (62.5 per cent) showed an elevation of blood-pressure in excess of 145 systolic, 90 diastolic; 11 (45.8 per cent) had definite hypertension. In all of the cases with definite hypertension there was marked thickening of the arteries in the scarred region of the kidneys, but only moderate arterial thickening was found in 4 of the 9 cases in which the blood-pressure was normal. In the other 5

cases with normal blood-pressure marked thickening of the arteries was present; but in 2 there was also extensive pyonephrosis, and the other 3 were relatively young individuals as compared with the patients who had definite hypertension.

The fact that localized renal lesions are not commonly found in cases of so-called essential hypertension must be emphasized. For example, in 100 cases of hypertension in which blood-pressure studies and urograms were made, chronic atrophic pyelonephritis was found in only 4 instances. Further urographic studies in a large series of cases of hypertension and studies of the effect of nephrectomy for other types of renal lesions as well as chronic atrophic pyelonephritis are advisable.

**Effect of Nephrectomy Upon Hypertension Associated with Organic Renal Disease**—In a study by Schroeder and Fish<sup>4</sup> of the effects of nephrectomy on patients exhibiting arterial hypertension associated with organic renal disease, 2 of 7 patients were improved for some time (11 and 16 months) following operation; 1 was temporarily improved; in 2, no change was observed; and 2 who were not improved have subsequently died. All remained actually or potentially hypertensive. Patients were selected in whom severe arterial hypertension was associated with unilateral renal disease accompanied by marked diminution of function of the affected kidney but not by renal insufficiency. Four cases showed evidence of disease of the opposite kidney of lesser degree; in 3 no other lesion was demonstrated. All kidneys removed showed, in addition to a variety of lesions, inflammatory and non-inflammatory, varying degrees of arterial and arteriolar sclerosis. The best results occurred in the cases with the

smallest degree of vascular disease. As was shown in 1 instance, there is no certainty, however, that the degree of vascular disease in 1 kidney is the same as that in the other.

That renal lesions are not the sole cause of arterial hypertension is evidenced by their presence when the arterial pressure is not elevated. Furthermore, continuance of the elevated blood-pressure after removal of the affected kidney may be explained by the part played by vascular or other disease in the remaining kidney. The 2 patients who died had pyelonephritis as well as vascular lesions. Recent investigation in rats by Wilson and Byrom<sup>5</sup> has shown that vascular disease in the unaffected kidney follows partial constriction of 1 renal artery.

The results of this study show that removal of a diseased kidney is not to be regarded as a procedure from which relief of hypertension can be expected to occur in all or in many cases. If arteriolar disease is secondary to the renal lesion or to hypertension and serves to maintain an elevated blood-pressure which was initiated in the first place by a renal lesion, it would appear possible sometimes to obtain improvement by nephrectomy. A successful result might be expected if the lesion were confined to 1 kidney, and if arteriolar sclerosis of the other kidney had not progressed to an irreversible degree. The following criteria for the selection of cases for nephrectomy are suggested: (1) The onset of arterial hypertension should be recent (arbitrarily, within 2 years); (2) the renal lesion should be confined to 1 kidney, with a diminution of function in that kidney; (3) renal functions, as measured by the ability of both kidneys to concentrate urine and by the urea clearance test, should be within normal limits; (4) retinitis should be absent,

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teries appeared to be normal. The thickening was not confined to the arterioles; it was also seen in the interlobular and arcuate arteries. It was partly due to increased thickening of the muscular coat and partly to extensive hyperplasia of the intima. It may be the result of: (1) Arteritis which is part of the chronic inflammatory reaction in the renal parenchyma; (2) contraction by the scar tissue, and (3) more distal obstruction to the capillaries associated with the destruction of the renal parenchyma.

A review of a consecutive series of 57 cases, in which a diagnosis of chronic atrophic pyelonephritis was made by

urographic examination, revealed that 26 (45.6 per cent) had a blood-pressure greater than 145 systolic, 90 diastolic. In a series of 24 cases in which chronic atrophic pyelonephritis was diagnosed pathologically after nephrectomy, 15 (62.5 per cent) showed an elevation of blood-pressure in excess of 145 systolic, 90 diastolic; 11 (45.8 per cent) had definite hypertension. In all of the cases with definite hypertension there was marked thickening of the arteries in the scarred region of the kidneys, but only moderate arterial thickening was found in 4 of the 9 cases in which the blood-pressure was normal. In the other 5

Tigerstedt and Bergman, in which renin was described. In repeating the experiments of Tigerstedt and Bergman, Merrill, Williams and Harrison<sup>8</sup> found that the increase in sensitivity to renin did not appear immediately after nephrectomy but only after elapse of a number of hours—which led to the belief that normal renal tissue might form some substance which was distributed in the body and which had the property of limiting the pressor effect of renin. Further indirect evidence for the existence of a renal antipressor substance is found in the experiments of Blalock and Levy, who showed that in an animal with unilateral ischemia removal of the normal kidney resulted in a marked rise in blood-pressure. Also, the observation of Katz, Rodbard, Steinitz, and Friedberg,<sup>9</sup> which indicated that renal hypertension is dependent on the ratio of ischemic to normal kidney tissue, is compatible with the hypothesis of the elaboration of an antipressor principle by the normal kidney. Additional support for the hypothesis of an antipressor substance has been furnished by experiments in which it was shown that extracts of normal kidneys tended on standing to lose their pressor property more rapidly than did similarly prepared extracts of ischemic kidney of the same animal.

Most convincing indirect evidence for the existence of a humoral antipressor substance is the observation by Harrison, Grollman, and Williams<sup>10</sup> that hypertensive pregnant animals commonly develop a well-marked decline in blood-pressure during the last part of pregnancy and that the blood-pressure increases to its previously elevated level following delivery; it seems probable that the fetus or the placenta forms some substance capable of reducing the elevated blood-pressure of the maternal organism. Direct evidence of the validity

of the hypothesis that the kidneys elaborate some substance which has the property of inhibiting the pressor effect of certain agents, including the renal pressor substance, renin, was obtained when it was found by Harrison, Grollman, and Williams<sup>10</sup> that extracts pre-

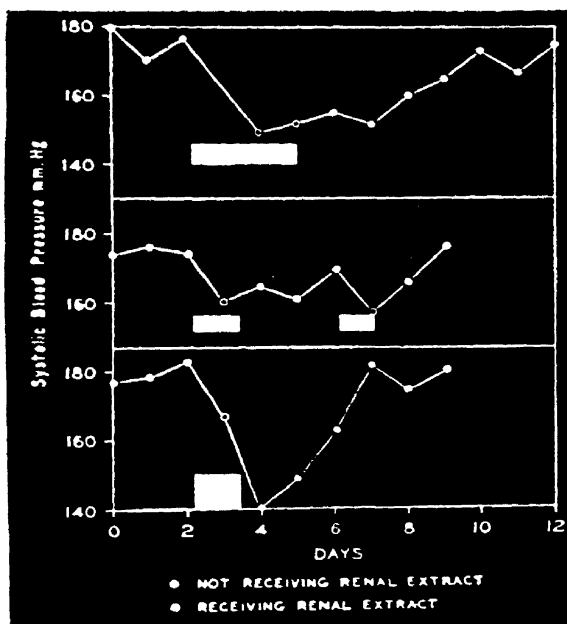


Chart I—Three different experiments, each involving use of 4 hypertensive rats. First experiment shows effect of feeding renal extract in a rather small dose over a period of several days. Second or middle curve depicts effect of administering small amounts of the extract for 1 day only on 2 separate occasions. Third or lowest curve illustrates result obtained when a relatively large amount of active principle was administered for a short period of time. In all instances decline in blood-pressure came on slowly and did not disappear for several days after extract had been discontinued (Harrison, Grollman, and Williams: *Am J. Physiol*)

pared from the kidneys of various animals did diminish the sensitivity of rats to renin and certain other pressor substances.

When extracts containing the renal antipressor substance were administered by Grollman, Williams, and Harrison in sufficient amount, either parenterally or orally, to rats rendered hypertensive by subtotal nephrectomy, a well-marked and prolonged decline in the blood-pressure

TABLE II  
COMPARISON OF SOME PROPERTIES OF THE RENAL ANTIPRESSOR SUBSTANCE WITH THOSE OF CERTAIN DEPRESSOR SUBSTANCES

Substance	Source	Hypotensive Effect on Experimental Animals				Oral Effectiveness Demonstrated	Precipitation by Ammonium Sulfate	Dialyzability	Comment
		Normal Animals		Hypertensive Animals					
		Decline	Duration	Decline	Duration				
Histamine	Nearly all tissues	+	Seconds or minutes	+	Seconds or minutes	0	0	+	No depressor effect in etherized rabbits
Acetyl-choline . . .	Many tissues	+	Seconds or minutes	+	Seconds or minutes	0	0	+	Depressor effect abolished by atropine
Adenosine (and related compounds)	Muscle, blood (all tissues)	+	Seconds or minutes	+	Seconds or minutes	0	0	+	Causes heart block in guinea-pigs
Urohypotensin (Abelous and Bardier)	Urine	+	Minutes	?	?	0	+	0	Constriction of pupil of rabbit's eyes (?)
Kallikrein (padutin) (Frey and Kraut)	Urine, pancreas	+	Seconds	?	?	0	+	+	Inactivated by blood
Depressan (detonin) (Wollheim and Lange)	Urine, posterior lobe of hypophysis	+	Minutes or hours	?	?	0	+	0	Absent from urine in essential hypertension: present in renal hypertension and in normal subjects
McDonald's depressor substance	Liver	+	Minutes or hours	?	?	0	?	?	Precipitated by phosphotungstic acid
Lange's depressor substance . .	Intestine, mesentery, nearly all tissues	+	Seconds or minutes	?	?	0	+	+	A guanidine derivative?
Depressor substance of Major and Weber	Brain	+	Minutes	?	?	0	?	?	Not precipitated by silver or by phosphotungstic acid
Substance of Euler and Gaddum	Intestine, brain	+	Seconds	?	?	0	0	+	Contraction of rabbit's intestine
Gomez's depressor substance . .	Renal cortex	?	?	?	?	0	?	?	Chemical properties and animal experiments not reported
Tubulin (Jablons) . . . .	Kidney	?	?	?	?	0	?	?	Animal experiments not reported
Renal antipressor substance* .	Kidney	0	0	+	Days	+	+	0	Precipitated by picric acid

\*Pharmacologic properties as given refer to effects obtained by oral administration.



occurred. When administered orally, the decline in blood-pressure set in slowly and lasted for a number of days after the animals had resumed normal diet (Chart I). Markedly hypertensive rats frequently appeared ill and occasionally died following a rapid decline of blood-pressure. At present it is uncertain whether such deleterious effects are due to impurities or to lowering of the blood-pressure *per se*. To induce in dogs the same decline in blood-pressure as occurred in rats, from 30 to 50 times as much material had to be given. These experiments seem to establish beyond question that animals with experimental renal hypertension respond to renal extracts with a decline in blood-pressure. The question as to whether such a decline is in fact desirable or undesirable, however, has not yet been clearly proved.

Of a small number of patients with advanced and severe hypertension who have been treated by administration of the renal antipressor substance orally or parenterally, a decline in the blood-pressure has been observed in most instances. The authors prefer, however, to draw no conclusions as regards the therapeutic effect in patients. The subjective improvement which seemed to occur might conceivably have been the effect of suggestion; and the possibility that the declines in blood-pressure were spontaneous has not been entirely excluded. At the present time extremely large amounts of kidney are required for the production of a single human dose; and there is no certain method of determining which patients have hypertension of renal origin (and it is only on such patients that the extract would be expected to be effective). Finally, since a marked decline in blood-pressure occurring after the administration of the extract in animals has frequently been associated with severe untoward symp-

toms, great caution must be used in the treatment of patients until more is known of the nature of this reaction.

The renal antipressor substance of Grollman, Williams, and Harrison differs in many respects from the depressor effects reported by other investigators, as shown in Table II. The chemical nature of the active principle of the extract is still uncertain (Grollman, Williams, and Harrison<sup>11</sup>). Under proper conditions of temperature, salt concentration and pH, the active principle is soluble in 40 per cent acetone and can be precipitated by the addition of further acetone in sufficient quantity; also it can be precipitated by the use of ammonium sulfate or by saturation with sodium chloride. No other substance has been described which has the properties of long duration of action, effectiveness by mouth, and lack of reduction of blood-pressure in normal animals as compared to marked reduction of blood-pressure in animals with renal hypertension.

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### CONGESTIVE HEART-FAILURE

**Combined Use of Ouabain and Digitalis**—A method of obtaining rapid digitalization by the simultaneous administration of ouabain intravenously and digitalis leaf by mouth has been presented by Batterman, Rose, and DeGraff.<sup>12</sup> Theoretic considerations concerning the production of complete digitalization with the accepted, rapid methods are shown schematically in curves A and B of Fig. 2. When a single dose of digitalis is given by mouth, there is a definite latent period of 2 to 5 hours before any effect is apparent, and 6 hours are required for the maximum effect to develop. When doses are repeated according to the Eggleston method, the full therapeutic effect is not manifest be-

fore 12 to 24 hours. On the other hand, by giving an initial dose of  $\frac{1}{130}$  grain (0.5 mg) of ouabain (g-Strophanthin) intravenously, and doses of  $\frac{1}{650}$  grain (0.1 mg.) at intervals of  $\frac{1}{2}$  to 1 hour thereafter, complete digitalization can be obtained in from  $1\frac{1}{2}$  to 3 hours. Ouabain,

Digitalization was produced 60 times in 59 patients, ranging between 28 and 79 years of age, with varying degrees of congestive heart-failure and different types of heart disease. Before digitalization the maximum effect of absolute rest in bed, the administration of oxygen and

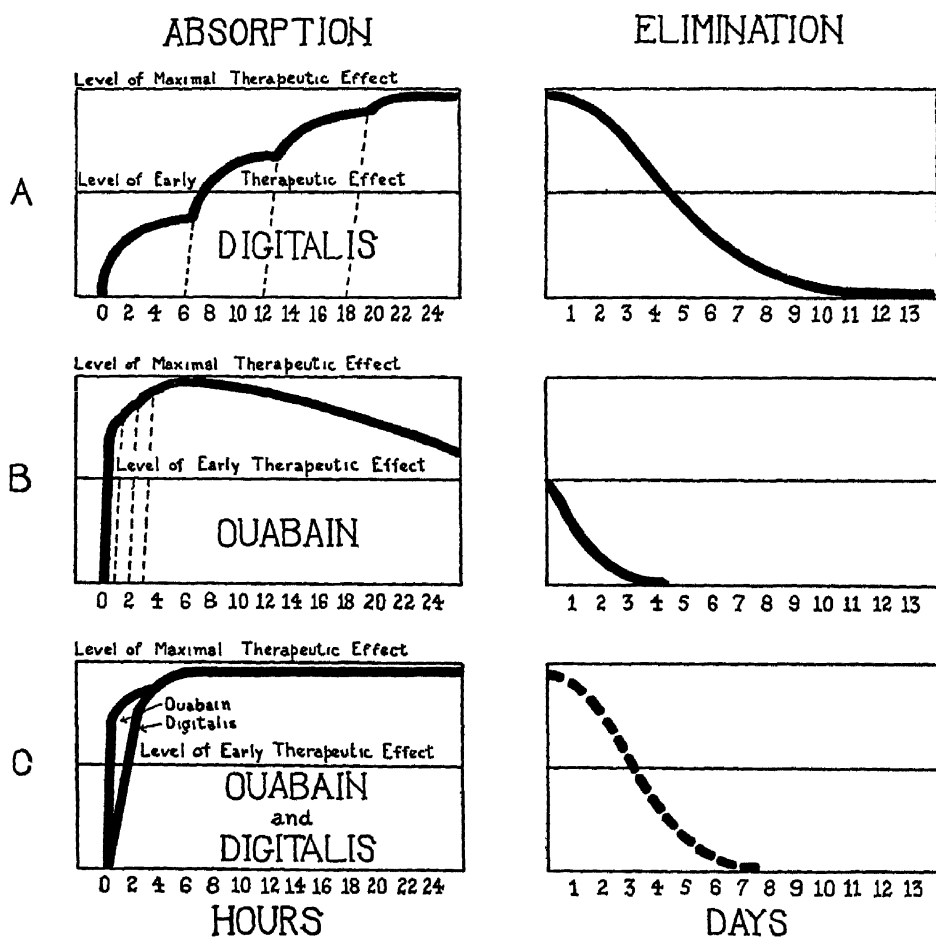


Fig. 2—Schematic representation of absorption and elimination, A, of digitalis leaf, given orally by method of Eggleston, B, ouabain, given intravenously by method of Wyckoff and Goldring; and C, digitalis and ouabain in combination (By elimination is meant persistence of digitalis effect upon ventricular rate of patients with auricular fibrillation.) Curve of "Elimination" in C (broken line) is at present under investigation. (Batterman, Rose, and DeGraff: *Am. Heart J.*)

however, has the disadvantage of being eliminated quickly. In their study Batterman and his associates have attempted to avoid the disadvantages of both by supplementing and maintaining the early action of ouabain by the simultaneous administration of a single dose of digitalis.

sedatives, limitation of fluid intake, and dietary restrictions was ascertained in each case. Simultaneously with 6 or 8 cat units of digitalis leaf by mouth, 0.5 mg. (5 cat units) of ouabain was then given intravenously. The amount of the digitalis (whole leaf) preparation depended on the estimated edema-free

weight of the patient. No other digitalis was given for 24 hours. At the end of this time the patient was placed on a daily maintenance dose of 1 to 2 cat units of digitalis leaf by mouth (It is important that only reliable preparations of ouabain and digitalis be used. Ouabain in solution undergoes deterioration; and, unless a recently standardized preparation is used, desired immediate effect of a dose might not be obtained.)

In the majority of instances, improvement occurred within 1 hour. With 1 exception, all of the rheumatic patients showed improvement within 1 hour. The early improvement in this group may be explained by the fact that so many of the patients had auricular fibrillation. All patients with arterial hypertension, uncomplicated by arteriosclerosis, were improved within 2 hours. However, when arteriosclerosis was an etiologic factor in the heart disease, in only approximately 70 per cent of the patients was improvement found within the first 2 hours. This effect, once established, was progressive, the maximum being attained at the end of 24 hours. After the initial digitalization, it was not difficult to establish the maintenance dose of digitalis leaf. The method was found to be applicable to patients with normal sinus rhythm as well as to those with auricular fibrillation. Eighty-three per cent of the patients with auricular fibrillation were improved within 1 hour; whereas only 58 per cent of those with normal sinus rhythm showed improvement in this period. In view of manifestations of mild toxicity presented by a small number of the patients, it is recommended that the dose of digitalis, with this method of treatment, be regulated as follows: For patients who weigh less than 125 lbs. (56.8 kg.), 6 grains (4 cat units, or 0.4 Gm.) should be administered; for those between 125

and 175 lbs. (56.8 to 8 kg.), 10 grains (6 cat units, or 0.6 Gm.); and for those over 175 lbs (8 kg.), 12½ grains (8 cat units, or 0.8 Gm.).

**Effect of Coramine in Certain Cardiac States**—In a study of a group of 10 cardiac patients with Cheyne-Stokes respiration or paroxysmal dyspnea, Stroud and Twaddle<sup>13</sup> found that the administration of coramine may have a beneficial effect on the abnormal respirations. Dramatic responses, however, usually did not follow oral administration of doses of ¾ to 1¼ drams (3 to 5 cc.), 4 to 5 times daily, but rather a slow progressive improvement occurred; usually 1 to 3 days elapsed before the optimum benefit was realized. Cardiac efficiency was not shown to be constantly improved from prolonged oral use of coramine. A more prompt but transient response followed the intravenous administration of 1¼ drams (5 cc.) doses, which may be attended by symptoms arising from widespread cerebral stimulation; decline in intrathecal pressure and, to a less constant or striking degree, a decline in venous pressure were observed. That these pressure changes are directly related to the clinical improvement, however, is considered doubtful. The conclusion is drawn that the direct action of coramine on cardiac efficiency is not marked, and that its favorable action on the respiratory distress of cardiac disease is the result of its stimulation, as a chemical agent, of the respiratory receptors, either peripherally or centrally.

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## CORONARY ARTERY DISEASE

### Mechanism of Coronary Artery Occlusion

For many years the formation of a thrombus on an arteriosclerotic plaque

was considered the sole cause of coronary artery closure. Studies during the past few years, however, have indicated that intramural hemorrhage in a sclerotic artery is an important factor in the production of such a lesion; it has been identified either as an immediate etiologic factor in acute occlusion by massive intimal hematoma, or as a precipitating agent in thrombosis of the lumen of the vessel. To ascertain the frequency of acute occlusion caused by intramural hemorrhage, and to compare it with the incidence of occlusion due to other causes, Horn and Finkelstein<sup>14</sup> have studied 100 unselected autopsy cases of acute occlusion of the coronary arteries. Particular attention was paid to the relative importance of intimal hemorrhage and primary thrombosis on an arteriosclerotic plaque in the pathogenesis of acute coronary occlusion, and also to the relationship between the extent of mural vascularization, hemorrhage, and intimal sclerosis.

In 62.5 per cent of the cases coronary artery occlusion was produced by intramural hemorrhage, and in 37.5 per cent by the formation of a thrombus on an arteriosclerotic plaque. The main branches of the coronary arterial tree were found to have advanced sclerotic changes with approximately equal frequency, although the incidence in the anterior descending branch of the left coronary artery was perhaps slightly higher than elsewhere. Only rarely did the intermuscular branches of the coronary arteries exhibit arteriosclerotic changes. Contrary to common belief, the individual artery most frequently the seat of acute occlusion was the right coronary artery (61 instances). Next to the right circumflex artery, the largest number of recent occlusions occurred in the anterior descending branch of the left coronary artery (56 instances);

27 and 15 recent occlusions, respectively, were found within the circumflex branch of the left coronary and the primary divisions of the anterior descending branch of the left coronary artery. Only 1 saccular aneurism was encountered, it involved the right coronary artery, and was associated with an extensive, recent, dissecting hemorrhage immediately bordering its distal limit. Simultaneous, multiple occlusions of the coronary arteries were common. In 3 cases a single recent occlusion caused death in individuals, with only moderate arteriosclerosis of the coronary arteries, in whom there was no evidence of previous myocardial infarction. In the majority of instances, however, acute arterial occlusion occurred in arteries which showed extensive sclerotic involvement, with associated narrowing of the lumina.

Vascularization of the intima was found only in the presence of arteriosclerosis, and was regarded as a sequel, not the basic cause, of the intimal degenerative changes. Once established, however, vascularization may be an important factor in the further advance of the arteriosclerotic process. Usually the extent and degree of atheromatous "abscess" formation in the intima were in inverse ratio to the vascularization. Intramural hemorrhage was observed frequently, and was always found to be associated with vascularization and plaque degeneration. The authors are of the opinion that it originated invariably within the wall, rather than by imbibition from the lumen. Intramural hemorrhage was found to lead to coronary artery occlusion either by inducing acute degeneration and reactive responses in the plaque overlying the hemorrhage, by obstructing the artery mechanically, or by actually producing dissolution and rupture of the intimal layer. The extent and variety of change were dependent

upon the relationship between the vascularity of the plaque and the degree of degeneration within.

Coronary artery occlusion produced by the deposition of a thrombus on a plaque was usually secondary to an edematous, acute, reactive or degenerative change in the subendothelial tissue. The coexistence of recent and organizing changes within a plaque or its thrombus supports the belief that coronary artery occlusion may be a slow, progressive process. Fibrinoid-like masses within arteriosclerotic plaques were considered to be the sequelae of intramural hemorrhage or extravasated blood plasma originating from the mural capillaries within the plaque; infiltration of blood from the main artery lumen was not believed to play an important part in such formations. Calcification was frequently found within degenerating plaques. The calcium deposits showed a predilection for the basal segments of the intima, but occasionally extended throughout the thickness of the intima and impinged upon the endothelium; usually the vascularization of the arterial wall in the vicinity of the calcified portion was sparse. Bone formation within the intima was found in 5 cases.

Distortion of the architecture of the wall produced by slow, progressive arteriosclerosis and repeated hemorrhage, with reactive vascular proliferation, rendered difficult the differentiation of arteriosclerotic narrowing from previous thrombotic occlusion. Medial atrophy was a frequent accompaniment of arteriosclerosis, and appeared to be in direct proportion to the thickness of the adjacent plaque—representing, in a sense, a pressure atrophy. And a prominent, adventitial, perivascular infiltration of lymphocytes was often encountered in arteriosclerotic vessels. Arteriosclerosis was observed in every instance of par-

tial or complete arterial occlusion. The morphologic analysis in this study showed coronary artery occlusion to be an incident in arteriosclerosis, but the direct, immediate, precipitating factors underlying recent occlusive changes could not be ascertained.

### Correlation of Symptoms and Pathology of Coronary Artery Disease

Correlation of the clinical manifestations and the pathologic findings in coronary artery disease often is difficult. Considerable light has been thrown on the subject, however, by the joint clinical and pathologic study by Blumgart, Schlesinger, and Davis<sup>15</sup> of 125 consecutive autopsy cases, in which particular attention was devoted to the pathologic basis for symptoms, the importance of collateral circulation in sustaining life in the presence of multiple areas of narrowings and occlusion within the coronary arteries, and the cause of death in cases of coronary artery disease. Thirty of the cases in which the hearts showed marked narrowing or occlusion of the coronary arteries, or myocardial infarction or fibrosis, or in which, during life, there had been definite evidences of angina pectoris, congestive failure, or myocardial infarction, were given more detailed study.

The technic used in injecting and dissecting the hearts, previously described by Schlesinger,<sup>16</sup> was briefly, as follows:

"The 2 coronary arteries were cannulated and injected simultaneously with different colored, radiopaque, warm (45° C.) lead-agar masses under a pressure of 150 mm. of mercury. A red-colored mass was injected into the right coronary artery, and a blue-colored mass into the left coronary artery. The mass was immediately hardened by immersion in iced salt solution, and the unfixed heart was *opened* by a series of incisions which unrolled the heart so that all of the coronary arteries lay in 1 plane. A *roentgenogram* of this preparation

# CARDIOVASCULAR SYSTEM

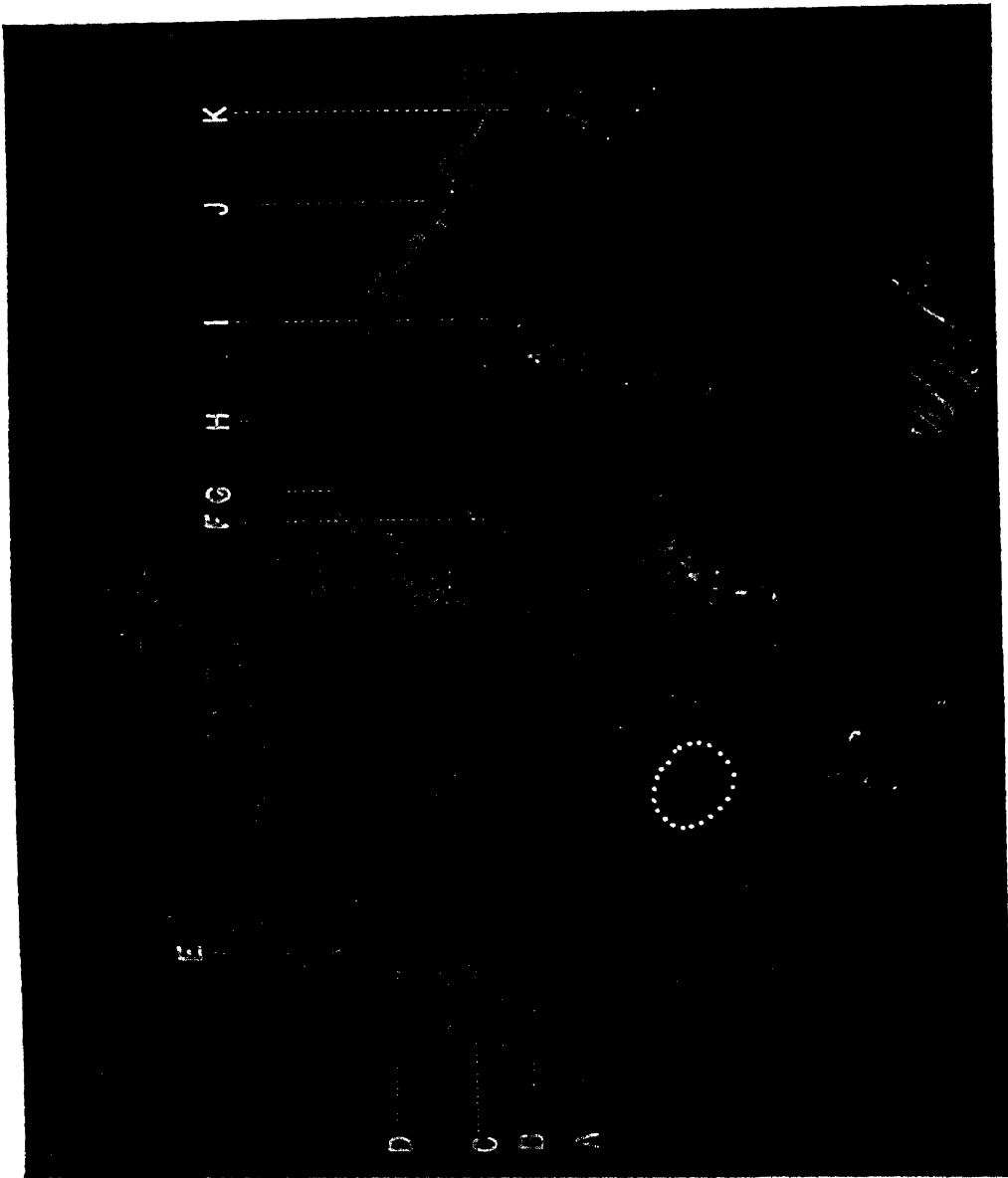


Fig 3—Copy of roentgenogram of injected and unrolled heart

A, B, C, D, E, F, I, K = complete occlusion

G, H = emboli

J = fresh thrombus.

(Blumgart, Schlesinger and Davis Am Heart J)

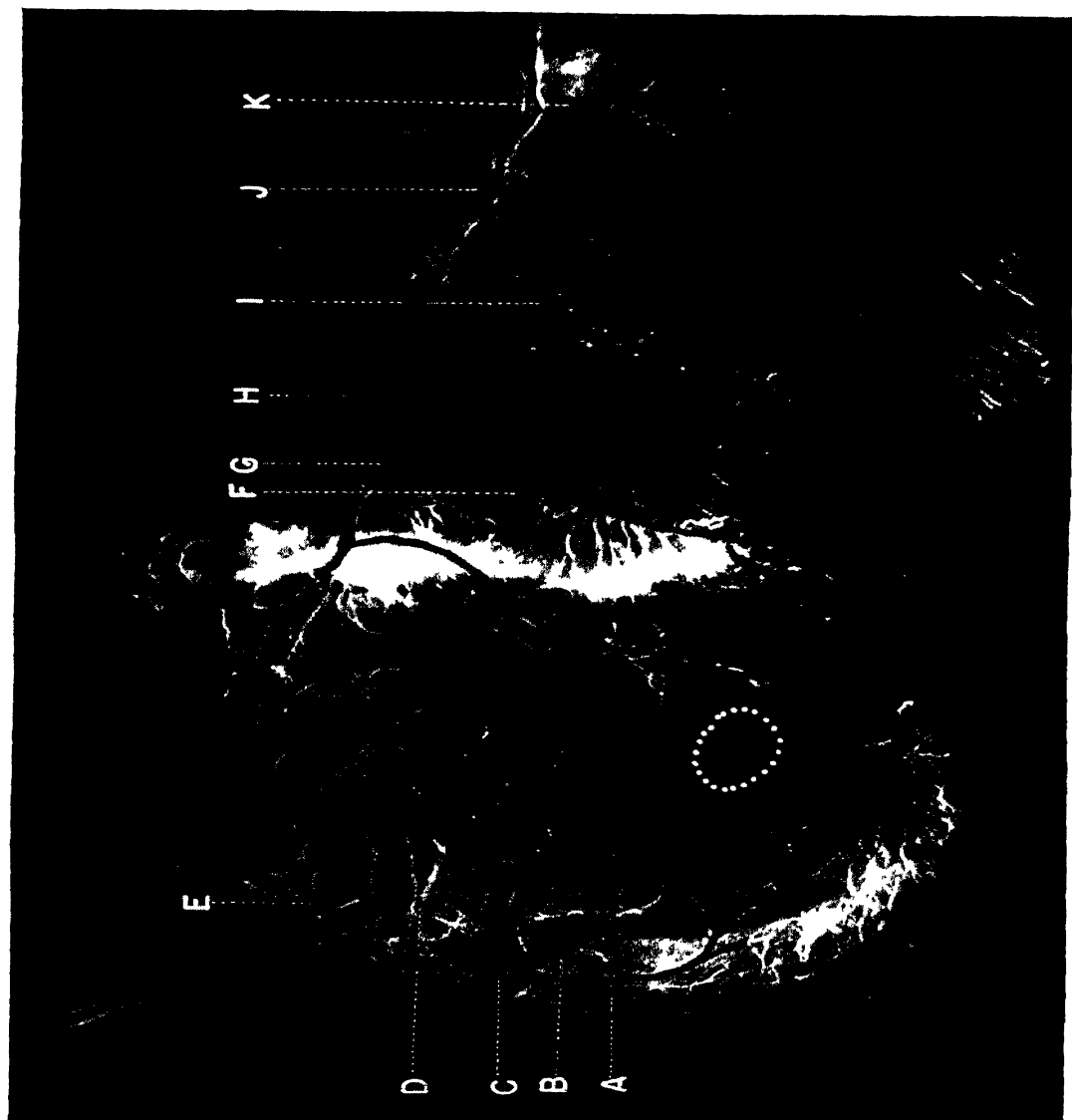


Fig. 4—Copy of roentgenogram of injected and unrolled heart, with arteries tinted to indicate color identified by dissection (Blumgart, Schlesinger and Davis Am Heart J )





was made. At no place in the roentgenogram of the unrolled heart was there a shadow of more than a single thickness of the cardiac wall. A complete *dissection* of the injected, unfixed arteries was then carried out in order to confirm, correct, or extend the observations recorded roentgenologically" (Figs. 3, 4, 5)

For some years following the studies of Cohnheim and von Schulthess-Rechberg (1881) it was believed that the coronary arteries were end arteries.

proximately 40 micra in diameter, however, do exist between the coronary arteries of normal hearts, their presence being demonstrable by the injection of watery solutions, but these fine communications are probably of little functional significance in obviating the untoward effects of sudden coronary narrowing or occlusion. Obstruction to normal coronary arterial blood flow by

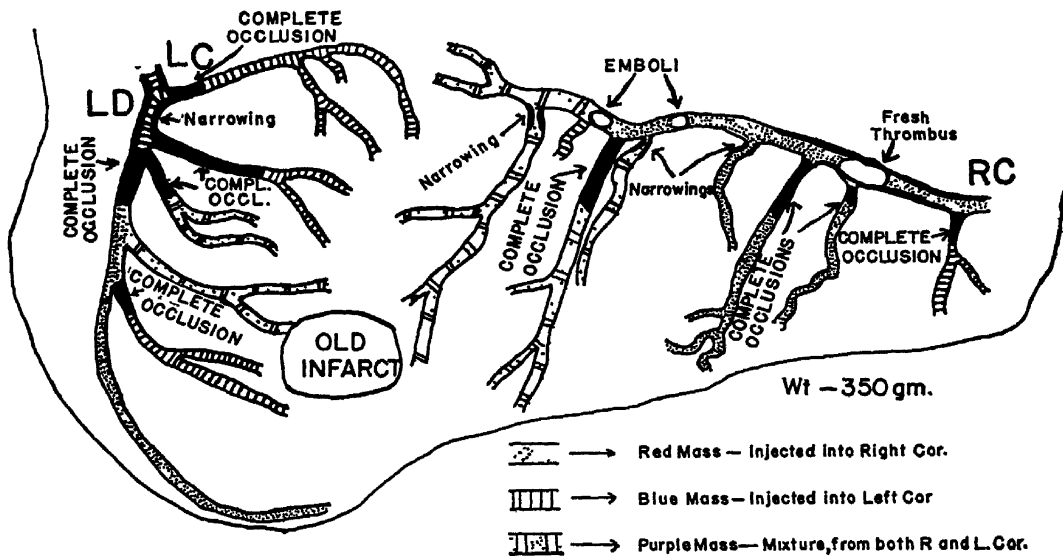


Fig 5—Diagram made by tracing Fig. 3 and indicating color as shown in Fig. 4, by cross-hatching for red, stippling for blue, and a mixture of both for purple. (Blumgart, Schlesinger and Davis Am. Heart J.)

Gradually it has become the consensus, however, that an anastomotic circulation exists within the heart, although difference of opinion exists as to the functional significance of such an anastomotic circulation, the circumstances which may lead to its development, and its exact anatomic architecture.

The study by Blumgart and his co-workers has revealed that, irrespective of the age of the individual, anastomoses measuring 40 micra, or more, in diameter, between the right and left coronary arteries, usually do not exist in the absence of partial or complete occlusions of these arteries. Anastomotic communications measuring less than ap-

arteriosclerotic narrowing or occlusion regularly results in the development of intercoronary anastomoses measuring 40 to 200 micra in diameter, which were clearly demonstrated by the injection of the lead-agar mass. It appears that in human hearts anastomotic circulation develops only *when* and *where* it is needed. The development of such anastomoses is not related to age, for they are not present in the hearts of even senile patients when little or no coronary arteriosclerosis is present. Such anastomotic circulation may compensate so well for occlusion or marked narrowing of a major coronary artery that the blood supply to the heart remains ade-

quate for the ordinary activities of life. When the narrowing or occlusion progresses so far that the coronary circulation is insufficient to meet the needs of the heart during periods of increased work, myocardial anoxemia results, *i e*, the "coronary reserve" is clearly reduced. The frequency of angina pectoris in patients who show such pathologic changes is in accord with these considerations.

In 10 of the 12 cases, out of the total of 125, in which uncomplicated *angina pectoris* was the primary condition, old, complete occlusions of at least 2 main coronary arteries were present. In 3 of these instances all 3 main arteries had been occluded, in the remaining 7, the 1 unoccluded coronary artery was markedly narrowed. In the 2 hearts in this group in which only 1 main coronary artery was completely occluded, the other 2 main arteries showed marked arteriosclerotic narrowing. In every case of angina pectoris the pathologic changes were in accord with the concept that angina pectoris is caused by paroxysmal, relative, myocardial ischemia, the maximum blood supply originally available to the myocardium had been obviously reduced by arterial occlusions or narrowing. Under such conditions, anything which further reduces the available blood supply or increases the nutritional requirements (oxygen, etc.) of the heart, or circumstances which increase the work of the heart beyond that which can be sustained by the reduced blood supply, lead to ischemia or anoxemia and pain. Factors which decrease the nutritional supply to the myocardium are (1) Narrowing and occlusion of the coronary arteries; (2) lowered blood-pressure, such as is observed in shock from any cause; also, the low diastolic blood-pressure in aortic insufficiency, (3) anoxia of the anemic

(anemia), stagnant (congestive failure), or anoxic types (pulmonary edema, etc.) Among conditions which increase the work of the heart and consequently increase its nutritional requirements are (1) Effort, (2) infection, (3) arterial hypertension, (4) cardiac hypertrophy, (5) valvular stenosis and insufficiency, (6) anoxia caused by pulmonary disease or anemia, and (7) tachycardia.

In 13 of the 125 cases recent or old coronary occlusions were found in the absence of angina pectoris, and in these cases only 12 main coronary arteries had been completely occluded before the final illness, which is in contrast to the fact that in the 12 cases of angina pectoris 25 main arteries were occluded. In 5 cases of angina pectoris complicated by antecedent or coincident congestive failure, or by valvular disease, there were, on the whole, relatively few occluded coronary arteries. In these instances angina pectoris and congestive failure were caused predominantly by the greatly increased load on the heart. 3 of the 5 patients had advanced rheumatic valvular disease, and 1 had *cor pulmonale*. In their hypertrophied hearts a collateral arterial circulation had developed. Thus, the presence or absence of pathologic changes in the coronary arteries was not always the sole factor which determined the presence or absence of angina pectoris or of coronary artery anastomoses. The findings suggest that constantly undernourished areas in hearts which are the seat of coronary arteriosclerosis, when subjected to still greater anoxemia, such as is brought about by exertion or emotion, undergo focal necrosis and a diffuse fibrous change, and that the replacement by connective tissue leads to myocardial weakness and congestive failure. The hearts with the greatest amount of replacement of myocardial fibers by

fibrous tissue were of patients who, after some months or years of angina pectoris, finally developed congestive failure.

A comparative study of the clinical characteristics of *coronary thrombosis* and those of *myocardial infarction* has brought the conclusion that coronary thrombosis and occlusion, *per se*, do not necessarily produce any characteristic clinical manifestations. If an occlusion occurs gradually, over months or years, with the concomitant development of an anastomotic circulation, no symptoms or signs will be produced and no myocardial lesions will be demonstrable. The syndrome usually called "*coronary occlusion*," which consists of prolonged substernal oppression or pain, a fall in blood-pressure, pallor, and the other manifestations of shock, and is accompanied by electrocardiographic changes, fever, leukocytosis, and an increased sedimentation rate, really signifies *myocardial infarction*, and should be so termed. Attacks of severe, prolonged pain, associated at times with collapse, may result, however, from prolonged insufficiency of the blood supply to the myocardium, and consequent anoxia—and may occur with or without simultaneous, or immediately preceding, coronary thrombosis. If such "*coronary failure*" is sufficiently prolonged, myocardial infarction results. In some instances, however, this may be obviated if the demands on the myocardium are quickly reduced by rest in bed, sedatives, or the control of rapid ventricular rates;—sufficient collateral blood flow may be available to satisfy the thus lowered cardiac requirements and permit recovery of the anoxic fibers. The duration of pain in such cases of coronary failure may be longer than that commonly seen in angina pectoris, but persistent electrocardiographic

changes, fever, leukocytosis, and an increased sedimentation rate, which are characteristic of myocardial infarction, are not found.

Although myocardial infarction may occur with or without simultaneous, or immediately preceding, coronary thrombosis or occlusion, the clinical diagnosis of *myocardial infarction caused by acute coronary thrombosis* would appear justified if the sudden, severe, crushing pain and collapse occur under circumstances in which the work of the heart is not increased, *i. e.*, during sleep or at rest, or under conditions, such as walking, which impose no greater burden on the heart than the patient has regularly borne satisfactorily in the past.

The clinical consequences of occlusions of the coronary arteries are significantly influenced by the original pattern of the coronary arteries in any given heart. Almost every possible variation in the length and importance of the 3 main coronary arterial branches was observed in this study. These variations could be classified into 3 general groups, *i. e.*, 1 with a balanced coronary circulation, and the other 2 with left and right coronary artery preponderance, respectively. The site of a myocardial infarct bears no necessarily constant and immediately obvious relationship to the location of an occlusion or occlusions in the coronary arteries. In some instances, rapid occlusion of a single, major, coronary artery in an otherwise normal heart will cause infarction of the region obviously supplied by this artery. But more often in hearts with an anastomotic circulation there is no such direct relationship; instead, they may show occlusion of the right coronary artery and infarction of an area in the left ventricle which is normally supplied by the left circumflex or by the left anterior descending artery. Simi-

larly, occlusion of the left circumflex or left anterior descending artery may cause infarction of an area normally supplied by the other artery. This paradoxical phenomenon is termed "*infarction at a distance*." In this study, in spite of a large number of instances of occlusion of the right coronary artery, no example of infarction confined to the right ventricle was found, which may be due to the fact the thin-walled right ventricle, like the auricles, may derive considerable nourishment from the blood within its cavity.

In the hearts of several patients in which the coronary blood flow was already reduced and presumably slowed because of occlusions and narrowing, the sudden fall in blood-pressure which accompanied postoperative shock evidently led to further stagnation, anoxemia, and the deposition of multiple coronary thrombi. That coronary thrombosis occurs so frequently during sleep, when, likewise, the blood-pressure is lowered, appears significant in this relation. Also, severe, progressive, congestive failure may predispose to coronary thrombosis. It is important, therefore, in cases of coronary arteriosclerosis, from whatever cause, to avoid a fall in blood-pressure.

In general, it may be concluded that *death* occurs whenever a sufficiently large area of the myocardium undergoes ischemia, with or without necrosis; or when, because of ischemia, asystole, ventricular fibrillation, or congestive failure occurs. Anoxemia, necrosis, infarction, and fibrosis of the myocardium, and their accompanying clinical manifestations, arise whenever there is a discrepancy between the nutritional requirements of the heart muscle, on the one hand, and the factors governing nutritional supply on the other. If the rate of development of narrowing and occlu-

sion exceeds that at which a collateral circulation can be elaborated, infarction results. *Rest in bed* for at least several weeks is advisable for patients, previously symptom-free, who suddenly develop *angina pectoris*, mild or severe, and for those patients who, having had *angina pectoris*, experience a sudden aggravation of symptoms. Patients who experience prolonged cardiac pain, but, on repeated examination, do not present fever, leukocytosis, increased sedimentation rate, or significant electrocardiographic changes may not require rest in bed for as long as 6 weeks.

### Relationship Between Coronary Sclerosis and Hypertensive Heart Disease

Significant facts pertaining to the relationship between essential hypertension and coronary arteriosclerosis have evolved from the studies directed by Davis and Klainer to (I) the incidence of coronary atherosclerosis in cases of essential hypertension<sup>17</sup>; (II) the rôle of hypertension *per se* in the development of coronary sclerosis;<sup>18</sup> (III) factors in the production of *angina pectoris*;<sup>19</sup> and (IV) factors in the production of congestive heart-failure in the course of hypertensive heart disease.<sup>20</sup> The studies were based on 137 patients (90 males, 47 females) with essential hypertension, 46 patients with hypertension of renal origin, and 324 patients (230 males, 94 females) with normal blood-pressure. All of the 507 subjects had been subjected to postmortem examination. In 100 additional cases the coronary vessels were studied by the injection-dissection technic of Schlesinger. Because of the relatively high incidence of coronary artery disease in diabetes mellitus, even in the absence of hypertension, patients with diabetes were excluded from the series.

At all ages, a significantly higher incidence of coronary sclerosis was found in the patients with essential hypertension (Chart II). The incidence of slight coronary disease was much higher, however, in patients without hypertension (Chart III). The percentage of

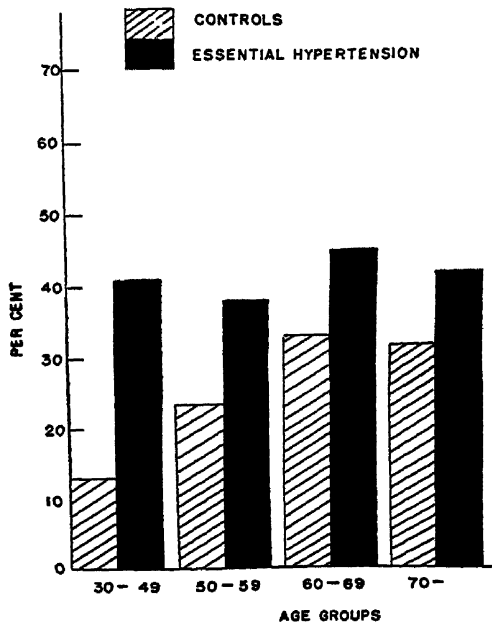


Chart II—Incidence of severe coronary disease. (Davis and Klainer Am. Heart J.)

cases of essential hypertension in which marked coronary disease was present was as high before, as it was after, the age of 50 years: Between the ages of 30 and 49 years, the incidence of severe disease in controls and in patients with essential hypertension was 15 per cent and 44 per cent, respectively, and at the age of 70 years, or more, 32 per cent and 44 per cent, respectively. The average for the 6 decades for patients with essential hypertension was 45 per cent; for the controls, 27 per cent, an increase over controls of 76 per cent. Men without hypertension presented much more coronary disease than women without hypertension, especially before the age of 60 years. Essential hypertension was found to increase the incidence of coro-

nary atherosclerosis proportionately in both sexes. In spite of the higher incidence of essential hypertension in women, the degree of coronary atherosclerosis in women with hypertension, however, remains significantly lower than in men with hypertension (Charts IV and V). Actually, women with hypertension show the same incidence of coronary disease as men without hypertension.

Although the incidence of coronary atherosclerosis in patients with essential hypertension is relatively high, hypertension, *per se*, is not the cause of this high incidence. Patients with severe hypertension, as evidenced both by the general blood-pressure level during life and by the extent of cardiac hypertrophy

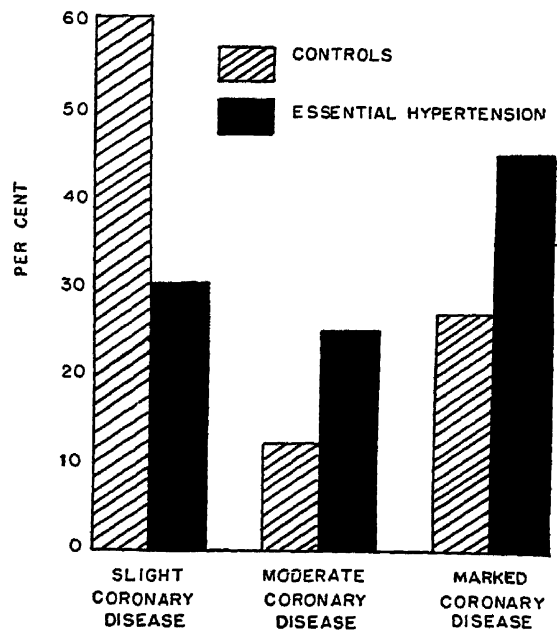


Chart III—Incidence of coronary disease. (Davis and Klainer: Am. Heart J.)

at necropsy, did not show any more coronary disease than did patients with mild degrees of hypertension; and the patients with hypertension caused by primary renal disease actually showed less coronary disease than a corresponding group of patients who did not have

hypertension. For reasons unknown, atherosclerosis occurs in varying degrees in different individuals, and in a given individual the distribution of the atherosclerotic process is irregular. Such patients develop atherosclerosis of the coronary arteries, although the degree of involvement may not be sufficient to cause symptoms; and if atherosclerosis

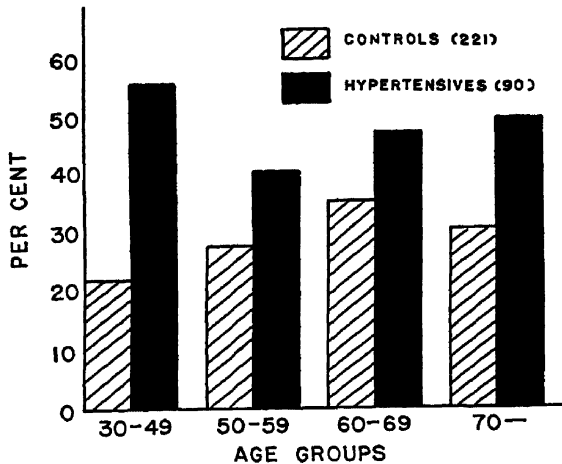


Chart IV—Marked coronary disease in males.  
(Davis and Klainer Am. Heart J.)

develops in certain other parts of the body, permanent hypertension may result. That interference with the blood supply to the kidneys or to the brain may produce hypertension is known; and, diminished blood supply to other structures, not yet studied, may do likewise. This hypothesis of a common etiologic factor explains the occurrence of marked coronary disease without hypertension and the high incidence of coronary sclerosis in patients with hypertension.

Comparison of the anatomic findings in 40 cases of *angina pectoris* with hypertension and in 21 cases of *angina pectoris* without hypertension revealed an extreme degree of coronary disease (involving 2 or more major arteries) in 95 per cent of the patients without hypertension, and in only 39 per cent of the patients with hypertension. The in-

cidence of myocardial infarction was correspondingly very much higher in the patients without hypertension. It is clear, therefore, that hypertensive heart disease predisposes to attacks of *angina pectoris* in patients with lesser degrees of coronary sclerosis. Two factors which favored the occurrence of *angina* in these patients were (1) cardiac hypertrophy and (2) increased cardiac work. In 80 per cent of the cases of essential hypertension a considerable degree of cardiac hypertrophy was present. It has been suggested by Wearn<sup>21</sup> that cardiac hypertrophy interferes with the nutrition of the heart muscle, in that the number of capillaries remains unchanged in spite of the increase in muscle mass. In addition, oxygen diffusion into the muscle fibers is probably impaired when the muscle fibers increase in thickness. Since congestive failure itself may be a factor in the production of hypertrophy, it was

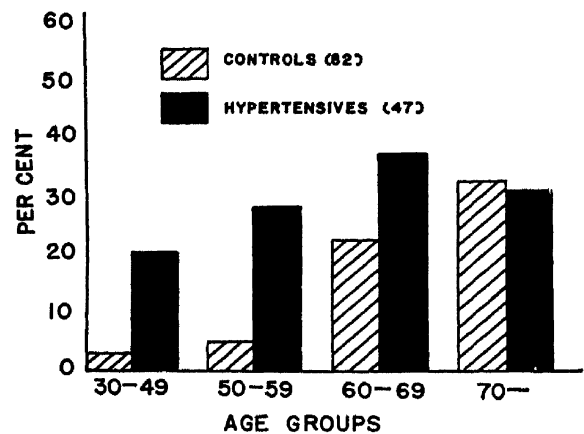


Chart V—Marked coronary disease in females.  
(Davis and Klainer Am. Heart J.)

impossible in many of the cases to ascertain how much of the hypertrophy was caused by the hypertension alone.

Comparison of the anatomic changes in 25 patients without hypertension and in 49 patients with essential hypertension, all of whom had congestive failure, revealed marked coronary artery disease in 23 (90 per cent), occlusion of

the major coronary arteries in 19 (76 per cent), and myocardial infarcts in 14 individuals (56 per cent) of the non-hypertensive (nonvalvular) group; in the hypertensive group, marked coronary disease was present in 26 (53 per cent), coronary occlusion in 16 (33 per cent), and myocardial infarction in 10 cases (20 per cent). These results show that factors other than coronary artery disease played an important part in heart-failure of hypertensive origin in at least 40 per cent of the cases. It is believed that congestive failure in hypertensive heart disease without marked coronary sclerosis results from increased cardiac work, direct muscle fiber injury, and anoxia. The sequence of events might be as follows: Increased cardiac work; direct muscle fiber injury, hypertrophy, anoxia resulting from both hypertrophy and increased cardiac work, muscle injury of anoxia origin, congestive failure, cardiac hypertrophy resulting from congestive failure, and further anoxia and muscle injury.

### Electrocardiogram During Attacks of Angina Pectoris

That changes in the electrocardiogram occur during attacks of angina pectoris is quite generally recognized, but opinions differ concerning the incidence, character and degree of these changes. Since angina pectoris is commonly regarded as a consequence of relative myocardial anoxia, it has been suggested that the early stages of coronary arteriosclerosis may be detected by tracings taken following exertion or generalized anoxia. Little attempt has been made, however, to compare the electrocardiographic response of patients with coronary artery disease with that of normal subjects under comparable conditions. The divergent results and conclusions may be attributed in part to the differ-

ent technics employed. Because of the short duration of the pain of angina pectoris, the different leads of electrocardiograms reported by various investigators as taken "during" attacks must necessarily have been taken at different times during the attack, and may represent entirely different aspects of the rapidly changing cardiovascular state. In view of these facts, Riseman, Waller and Brown<sup>22</sup> have made an electrocardiographic study of 20 patients with angina pectoris (16 men and 4 women, 5 of whom had arterial hypertension) and 15 normal subjects (10 of whom were between 25 and 31 years of age and 5 from 48 to 73 years of age) (1) to observe the relationship of electrocardiographic changes to the onset and cessation of pain by taking tracings *continuously* before, during and after attacks of angina induced first by exercise, and later by generalized anoxemia; (2) to investigate the mechanism producing these changes; and (3) to evaluate the diagnostic significance of the electrocardiographic changes induced by exercise or by generalized anoxemia.

The literature since 1918 reveals reports of 25 cases of angina pectoris in which electrocardiograms were taken during *spontaneous attacks*. In 19 patients changes in the S-T segment occurred during the attack; these changes consisted of an elevation or depression of the entire segment, or the take-off, in 1 or more of the 3 standard leads. Also, changes in the T-wave occurred in 19: a decrease of voltage occurred in 18 patients, 11 of whom developed inversion; 1 patient showed an increase in the voltage of the T-wave in 1 lead. There are available reports of observations of the electrocardiogram *following exercise* on more than 215 patients with angina pectoris. In different patients the exercise varied from simple knee-bend-

ing or raising dumbbells to running up as many as 8 flights of stairs; not all developed angina under these conditions. No attention was paid to the temperature of the environment. Changes in the S-T segment after exercise were shown by at least 93 of the 215 subjects. Changes in the T-waves were not analyzed by all investigators; apparently, 42 of the 215 subjects showed no changes in the contour of the complexes following exercise. The effect of *induced anoxemia* on the electrocardiogram has been studied in 56 cases of angina pectoris. Not all of the patients developed angina under the conditions of the studies. Changes in the S-T segment occurred in 28 subjects. Variations in the T-waves were not analyzed by all investigators.

In the study by Riseman and his co-workers the exercise consisted of mounting and descending a 2-step staircase 20 times (20 trips). An electrocardiographic tracing was taken for 1 full minute with the patient standing at rest, and was *continued without interruption* throughout the exercise, throughout the attack of induced pain, and for 1 or more minutes after the pain had disappeared. Only 1 attack and 1 electrocardiographic lead were studied on any given day. Generalized anoxia was induced in 16 of the 20 patients with angina pectoris according to the method described by Rothschild and Kissin. These patients re-breathed room air for 8 to 15 minutes, and, as a result, lowered the oxygen content of the inspired air to between 8 and 10 per cent; the re-breathing was stopped either when the patient developed pain or when the spirometer was emptied. Anoxia was also induced in 5 of the patients with angina by having them breathe an atmosphere of fixed, low-oxygen content for 10 minutes, or until precordial pain was

experienced; the subjects, while at rest in the recumbent position, breathed from a large spirometer containing room air so diluted with nitrogen that it contained approximately 10 per cent oxygen, the valves being arranged to prevent re-breathing. Electrocardiographic tracings were taken *continuously* during these experiments. The precordial lead was studied in each patient, for the greatest changes following exercise occurred in this lead; in some instances 1 of the standard leads which had shown marked changes following exertion was also studied (usually Lead II). Variations of less than 0.1 millivolt in the voltage of the P- or T-waves or in the level of the S-T segment, changes of less than 0.3 millivolt in the QRS voltage (measured as the sum of the positive and negative excursions), and changes of less than 0.04 second in the duration of the P-R interval were ignored because of the difficulty in measuring accurately.

Changes in the electrocardiogram began long before the onset of the attack, increased until the exercise or anoxemia was discontinued, and then frequently assumed a somewhat different character. Before and immediately after the onset of angina the commonest alteration was a change, usually a depression, in the level of the S-T segment; less frequently there occurred a change in the voltage of the T-wave, which only rarely became diphasic or inverted. These changes were most frequent and most striking in the precordial lead. The magnitude of the S-T changes (occurring usually in the first third of the segment) following exertion varied from 0.1 to 0.15 millivolt in 31, and from 0.15 to 0.3 millivolt in 19 tracings; in all of the latter there was a depression. The magnitude of the T-wave changes following exertion varied from 0.1 to 0.15 millivolt in 22, and from 0.15 to



0.55 millivolt in the remaining 11 instances. Changes in the QRS and P-waves and the P-R interval were uncommon and usually of slight degree. Cardiac pain continued for 15 to 150 seconds after the cessation of exercise. Toward the end of the attack, and, also, after the disappearance of pain, the changes in the S-T segment tended to diminish or disappear in most instances, whereas T-wave changes became more pronounced; at this time half of the patients developed diphasic T-waves in 1 or more leads.

The onset of the electrocardiographic changes induced by exertion could be delayed by having the patients breathe undiluted oxygen before and during the exercise (which finding is in accord with the theory that myocardial anoxemia and its sequelae are the cause of anginal pain). In the 4 patients studied the minimum amount of exertion necessary to induce electrocardiographic changes proved to be 17, 25, 40 and 60 per cent, respectively, of the amount of work necessary to induce pain. When these patients, however, performed the same amount of exercise while breathing pure oxygen, 3 of the 4 showed no electrocardiographic changes; breathing oxygen under the same conditions failed to prevent the electrocardiographic changes induced by 5 to 10 trips more than the minimum necessary to cause changes when breathing room air.

Since the changes in the electrocardiogram began before the onset of pain and, in many instances, persisted or increased after the pain subsided, the conclusion is drawn that the changes are not characteristic or diagnostic of the attack of pain observed. Furthermore, similar changes can be induced in normal persons who have no heart disease. Only if the response of normal subjects differs materially from that of patients with

angina can electrocardiographic changes following exertion be used as objective evidence of angina pectoris. Survey of the literature, however, does not reveal sufficient information concerning the electrocardiographic response of normal individuals and also of patients with angina after *identical* exertion.

In the study, the 15 normal subjects after exercise (20 trips) showed changes in the electrocardiograms which were similar to those observed in the 15 patients with angina pectoris in some respects, and different in others. An increase in the voltage of the P-wave occurred in 5 subjects. Changes in the level of the S-T segment not exceeding 1 mm. occurred in 10 subjects; the remaining 5 developed changes in the S-T level of 0.5 mm., or less. A decrease of 2 to 7 mm. in the amplitude of the T-wave occurred in 13 subjects; no patient developed an increase in the voltage of the T-wave. Six subjects showed a definite notching, amounting almost to a reduplication of the T-wave, following exercise; a similar degree of notching was not observed in patients with angina, except occasionally when exercise was performed following medication. The changes in the 10 young normal individuals were not materially different from those observed in the 5 older subjects without heart disease, except that 4 of the young normals developed a decrease of more than 5 mm. in T-wave amplitude, whereas only 1 of the older subjects showed a similarly large decrease. In general, patients with angina pectoris are more likely to develop a depression of the S-T segment of more than 1.5 mm., or an increase in the voltage of the T-wave. On the other hand, patients with angina are less likely to show an increase in the voltage of the P-wave, or a marked decrease in the voltage or a deep notching of the T-

wave This marked decrease in T-wave voltage and the changes in the S-T segments in young normals after exertion are probably the expression of the local oxygen debt which follows muscular activity.

Changes in the electrocardiogram *after exertion* thus appear to be of little practical value in the diagnosis of angina pectoris or coronary artery disease, for some subjects without heart disease may show changes similar to those which occur in some patients with angina pectoris, whereas other patients with angina may fail to develop appreciable electrocardiographic changes following the same amount of work. The abnormalities in the electrocardiogram during and after an attack of angina pectoris following exertion may simulate also those which occur in cases of coronary artery occlusion. A single tracing taken to establish the diagnosis of myocardial infarction is of little value and, in fact, may give false information unless the patient has been at rest and has experienced no angina for some time (at least 15 minutes, and longer in some instances) before the tracing is recorded.

Changes in the electrocardiogram *during generalized anoxemia* also appear to be of little practical value in differential diagnosis, for the difference between the normal and abnormal responses is not sufficiently marked to avoid serious error. With the re-breathing method of Rothschild and Kissen slight precordial distress was induced in only 1 of 16 patients, although attacks could be induced regularly in all of these patients by the standardized exercise tolerance test. When anoxemia was induced by breathing, an atmosphere of constantly low oxygen content, 4 of the 5 patients developed precordial pain similar to that experienced in daily life or during the standardized exercise tol-

erance test; and all 5 developed changes in the electrocardiogram which were similar in all respects, except for heart rate, to those observed in the *same* patients during attacks induced by exercise. While breathing an atmosphere containing approximately 10 per cent oxygen, all 5 patients developed a change of at least 1 mm. in the level of the S-T segment; 2 patients developed a depression of 2 and  $2\frac{1}{2}$  mm., respectively (1 of whom showed evidence of coronary artery disease in the standard 4-lead electrocardiogram taken at rest, *viz.*, diphasic T-waves in Leads I, II and IV). Changes in the T-waves occurred in 2 of the 5 patients; no patient developed a diphasic or inverted T-wave as a result of anoxia, but the 1 patient who had a diphasic  $T_4$  during rest showed an accentuation of this phenomenon as a result of the S-T depression. Three of the 8 normal subjects developed a change of 1 mm. in the S-T level; none showed a greater change. Seven showed a decrease of 0.2 to 0.5 millivolt in the voltage of the T-wave; no subject developed an inverted or diphasic T in Lead IV R.

In the opinion of the authors, the technical difficulties and the possible dangers, especially in patients with arteriosclerosis of the coronary or cerebral vessels, also are definite drawbacks to general use of an anoxemia test. No untoward effects were experienced, however, by the subjects studied in the present investigation. The constant, watchful attention of 2 observers was necessary, however, throughout the test. The possibility of precipitating an attack of angina or pulmonary edema in a patient who may be unable to give adequate warning, together with the lack of evidence of any clear-cut difference between the responses of normal and an-

gina patients, have led to discontinuance of further tests.

### Coronary Insufficiency

**Modifying Action of Aminophylline, Nitrites and Digitalis Upon the Effects of Induced Anoxemia**—The modifying action of certain drugs upon the time and appearance of pain and upon the form of the electrocardiogram during anoxemia induced by breathing a mixture containing 10 per cent oxygen and 90 per cent nitrogen has been studied by Levy, Bruenn and Williams<sup>23</sup> on 10 patients (9 men and 1 woman, ranging in age from 47 to 69 years) with coronary sclerosis who had been followed for months or years in the wards and outpatient department of the Presbyterian Hospital, New York. Each patient had suffered from spontaneous attacks of anginal pain and obtained relief from nitroglycerin.

In a previous study, Levy and his co-workers (Levy, Bruenn and Russell)<sup>24</sup> established the following criteria for normal and abnormal electrocardiographic responses following the induction of generalized anoxemia:

*Normal*—(1) The RS-T junction is not displaced more than 1 mm. in any lead.

(2) The T-waves tend to decrease in amplitude.

(3) Partial or complete reversal of the direction of T in Lead I or Lead IV F, or both, in the absence of any RS-T displacement in these leads, is of uncertain significance. It was observed in 2 of 66 supposedly normal persons.

(4) Partial or complete reversal of the direction of T in Lead II or Lead III, or both, even though associated with RS-T displacement of less than 1 mm., is of no significance. It was observed in 22 of 66 supposedly normal persons.

*Abnormal*—(1) A change in the level of the RS-T junction of more than 1 mm. in any lead, even though unassociated with changes in the T-waves, is abnormal. Its importance is increased if combined with partial or com-

plete reversal in the direction of T in Leads I or IV F, or both.

(2) Partial or complete reversal in the direction of T in Lead I is abnormal when associated with any displacement of the RS-T junction in this lead. Such displacement may be as little as 0.5 mm.

(3) Complete reversal in the direction of T in Lead IV F is always abnormal.

(4) Partial reversal of the direction of T in Lead IV F, associated with any displacement of the RS-T junction in this lead, is abnormal. Such RS-T displacement may be as little as 0.5 mm.

*Aminophylline* (theophylline ethylenediamine), injected intravenously, in doses of  $7\frac{1}{2}$  grains (0.48 Gm.), caused a prolongation of 63 per cent in the time of appearance of anginal pain; RS-T deviation was diminished by 58 per cent; the T-waves were modified in 7 of the 10 cases (Fig. 6). The heart rate decreased twice and in no case was the rate accelerated; the systolic blood-pressure rose once, fell 3 times and did not change 4 times. The effects of an intravenous injection were of short duration, lasting, on the average, 20 minutes. In doses of 3 grains (0.2 Gm.), administered by mouth 4 times daily for 1 week, aminophylline caused a prolongation of 26 per cent in the time of appearance of pain; RS-T deviation was diminished by 32 per cent; and the T-waves were modified in 4 of 10 cases. It appears that when taken by mouth in adequate doses, the drug exerts a differential action in certain cases of cardiac pain by causing dilatation of the coronary vessels; the result probably depends, in part, upon the anatomic condition and physiologic state of the coronary circulation. Lactose, used as a control, caused no significant prolongation in the time of appearance of pain (2 per cent); the change in RS-T deviation was likewise small (13 per cent); and

the T-waves were modified in 4 of 10 cases.

*Nitroglycerin*,  $\frac{1}{100}$  gr. (0.0006 Gm.) tablet, dissolved in the mouth, caused a prolongation of 51 per cent in the time of appearance of pain; RS-T deviation was diminished by 47 per cent; and the T-waves were modified in 6 of 9 cases.

RS-T deviation was diminished by 26 per cent; the T-waves were modified in 4 of 9 cases; and the blood-pressure rose in 5, fell in 2, and did not change in 2 cases.

After the administration of 22.5 grains (1.5 Gm. or 15 cat units) of *digitalis* in 4 days, the usual changes in the

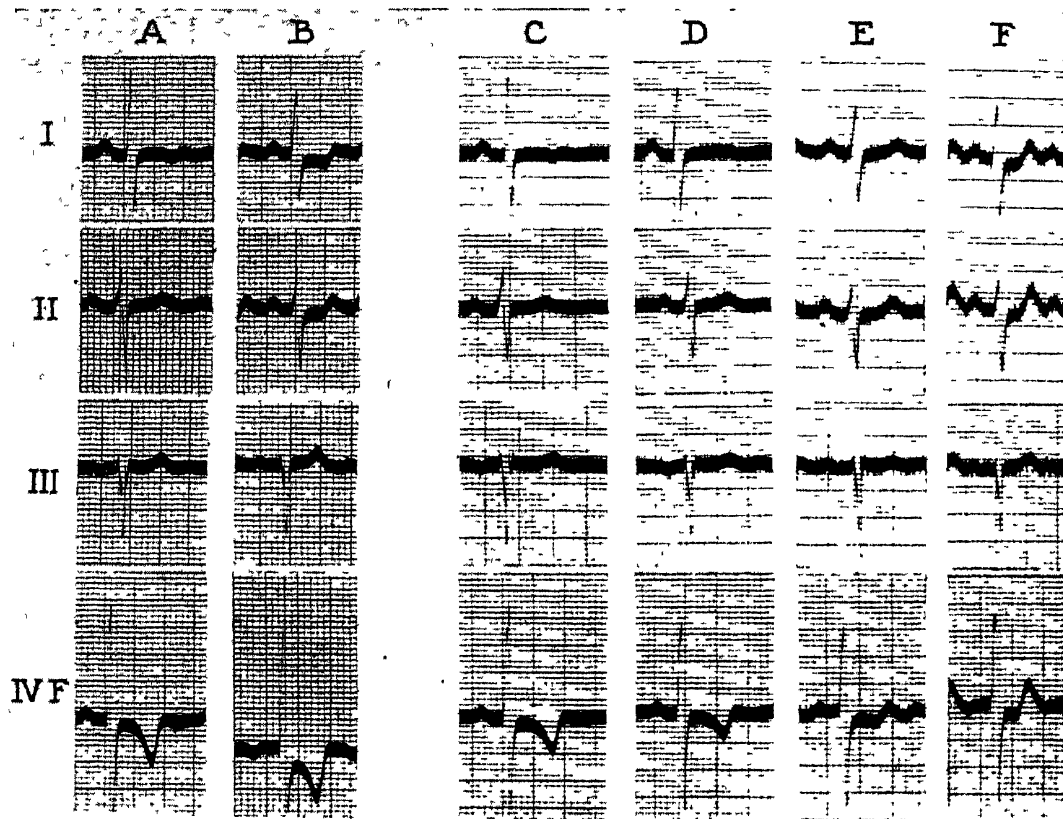


Fig. 6—Case 8 Male, aged 54 years. A, Control; B, after anoxemia for 7 minutes, pain. C, Control, D, immediately after intravenous injection of 0.48 Gm. aminophyllin. Anoxemia then started. E, After 10 minutes; F, after 20 minutes; slight pain. (Levy, Bruenn and Williams: Am. Heart J.)

The heart rate increased in 3, decreased in 2, and was unchanged in 4 cases; and the blood-pressure rose in 2, fell in 6, and was unchanged in 1 case. There were no constant relationships between changes in heart rate, blood-pressure, the occurrence of anginal pain, and changes in the electrocardiogram. *Erythrol tetranitrate*, in contrast to nitroglycerin, caused no significant prolongation in the time of appearance of pain (2 per cent);

RS-T junctions and T-waves appeared in the electrocardiograms. It was not clear whether the action of the drug tended to lessen or to accentuate changes in the form of the electrocardiogram which appear as a result of anoxemia. Occasionally the susceptibility to the pain induced by anoxemia was increased by digitalis. This effect does not appear to be due to coronary constriction; whether it is caused

by modification of cardiac output, or by some other action of the drug, was not shown by the study.

The clinical observations of Levy, Bruenn and Williams have received support in the study by Scott, Leslie and Mulinos<sup>25</sup> of the effects of anoxemia, after coronary artery ligation, on the electrocardiogram of the cat. Under sodium pentobarbital anesthesia (30 mg. per kg., administered intraperitoneally), anoxemia was induced in 14 cats, by the administration of an atmosphere containing 10 per cent oxygen, before, and at intervals after, ligation of the left branch of the left anterior descending coronary artery. In 12 of the 14 cats the RS-T segment of the electrocardiogram, which was unaffected by preoperative induction of anoxemia, was made to increase in deviation by postoperative induction of anoxemia. In 10 instances the RS-T segment returned to an isoelectric position in an average of 20 days, despite the persistence of the infarct (as shown at autopsy); and in 9 of this number the deviation originally produced by coronary ligation was reproduced by anoxemia. Control observations disclosed that the changes observed were not caused by anesthesia, change in blood-pressure, or pericardiotomy alone. Since the electrocardiogram frequently resumed normal contours when a fibrotic area was present, it is suggested that the electrocardiographic changes were caused by the local myocardial anoxia, and not merely by an area of scarred tissue.

#### **Effects of Certain Drugs on Coronary Blood Flow of the Trained Dog**

The effect of certain drugs on the coronary blood flow of trained dogs has been studied by Essex, Wegria, Herrick and Mann<sup>26</sup> by means of the thermotromuhr. The thermotromuhr is the

only method that permits continuous observations on coronary blood flow in the absence of complicating factors such as general anesthesia, artificial respiration, and procedures as inserting canulas into the heart or its vessels. Following a period of training which had accustomed the dogs to lie quietly on the laboratory table, the thermotromuhr units were placed on the coronary arteries with the animals under general anesthesia and with the use of sterile technic. After the animal had recovered from the immediate effects of the operation, which usually required from 24 to 48 hours, observations on the effects of the various drugs were begun.

Drugs that are known to lower blood-pressure, such as theophylline ethylenediamine (aminophylline), histamine, muscle adenosine phosphoric acid, acetyl-beta-methylcholine chloride (methylol), nitroglycerin, and papaverine, when administered in proportionate doses, markedly increased the coronary flow. With certain of these drugs the increase in flow was as great as 200 to 300 per cent. The augmentation of flow was accompanied by an acceleration of the heart rate. Coramine (pyridine beta-carbonic acid diethylamide), which may raise the blood-pressure under certain conditions, caused an increase in the coronary flow. Among the drugs that usually raise blood-pressure, pitressin (pressor principle of the posterior pituitary) decreased the coronary blood flow as much as 80 per cent and lowered the heart rate.

*Theophylline ethylenediamine* (aminophylline), in doses of from 120 to 240 mg., produced an increase of from 15 to 173 per cent in the flow in the left coronary artery; and with similar and larger doses, the flow in the right coronary artery increased by amounts rang-

ing from 29 to 161 per cent. In both vessels the duration of the effect was variable; in some cases the flow had returned to the control value within 2 minutes, whereas, in others, the flow remained increased for as long as 24 minutes after the injection. *Histamine acid phosphate*, in doses of from 0.1 to 0.5 mg., caused increases in flow varying from 155 to 239 per cent in the left coronary artery, the major effect usually disappearing within 3 minutes following the injection. *Muscle adenosine phosphoric acid*, in doses of from 10 to 20 mg., augmented the left coronary flow by as much as from 145 to 333 per cent, the flow returning to the control value within 3 minutes. In 1 experiment an injection of 0.2 mg. of *acetyl-beta-methylcholine chloride* (mecholyl) caused an increase of 95 per cent in the left coronary artery flow. *Nitroglycerin*, in doses of from 0.65 to 1.3 mg., caused increases in flow in both coronary arteries; the augmentation in the right coronary varied from 30 to 100 per cent, and that in the left from 35 to 72 per cent, the effect lasting from 1 to 3 minutes. *Papaverine*, in doses of 20 and 15 mg., increased both the right and left coronary flow by 52 and 93 per cent, respectively. *Coramine* (pyridine beta-carbonic acid diethylamide), in doses of 125 to 250 mg., caused an increase of 71 to 133 per cent in the blood flow through the left coronary artery, the effect lasting for from 7 to 14 minutes; a dose of 375 mg. caused a 73 per cent increase in the flow in the right coronary artery, but recovery from the effect of the drug was complete in 4 minutes.

That *epinephrine* in proper doses increases coronary blood flow is well established, but the mechanism by which this result is accomplished is still uncertain. Doses of from 0.025 to 0.05 cc.

of a 1:1,000 solution caused increases in flow of from 68 to 209 per cent in the right coronary artery, with the effect lasting for from 1 to 8 minutes. Doses varying from 0.2 cc. of a 1:100,000 solution to 0.1 cc. of a 1:1,000 solution caused an increase in flow of from 28 to 74 per cent in the left coronary artery. In 1 experiment an intravenous injection of 2 mg. of *atropine sulfate* increased the flow in the left coronary artery by as much as 86 per cent, and the flow was 25 per cent above the control level at the end of 49 minutes; and in 4 experiments intravenous doses of from 1 to 2 mg. caused an increase in flow of from 19 to 76 per cent in the right coronary artery, with the effect lasting 12 to 18 minutes or longer. An increased pulse rate was an invariable accompaniment of the increased coronary flow.

In 1 experiment an intravenous injection of 300 mg. of *pentobarbital sodium* (nembutal) produced a maximal increase of 60 per cent in the blood flow in the right coronary artery; and the flow was 15 per cent above the control level at the end of 82 minutes. In all probability the increase in coronary blood flow was part of the general vasodilator action of the barbiturate.

Intravenous injection of from 0.5 to 2 pressor units of *pitressin* (pressor principle of the posterior pituitary) caused immediate profound decreases (from 64 to 82 per cent) in right and left coronary blood flow; the maximal decrease was of short duration, but the flow remained below the control level for as long as 45 minutes. Since posterior pituitary preparations are widely used in obstetrics and roentgenology, their action in reducing coronary flow, as well as the circulation in other vessels, should be stressed.

## BENZEDRINE AND PAREDRIE, EFFECT ON CIRCULATION, METABOLISM AND RESPIRATION

The effects of benzedrine ( $\beta$ -phenylisopropylamine sulfate) and paredrine (p-hydroxy-a-methylphenylethylamine hydrobromide) on the circulation, metabolism and respiration have been studied by Altschule and Iglauer<sup>27</sup> in 14 normal persons and 1 with partial heart block due to coronary artery sclerosis. In doses of 20 mg. or more each drug caused a marked rise in systolic and diastolic blood-pressures, without any change in cardiac output, pulmonary circulation time, vital capacity, basal metabolic rate and respiratory dynamics. In several instances, transitory slowing of the pulse occurred at the onset of the rise in arterial pressure due apparently to a vagal reflex; in some such cases a transitory slight decrease in cardiac output was also detected. It is believed that the generalized increase of venous pressure following oral, intramuscular or intravenous administration of paredrine is due to active constriction of the veins produced by local stimulation, and that the venous constriction is not a factor in the production of arterial hypertension (Iglauer and Altschule).<sup>28</sup> Benzedrine in doses ordinarily used clinically for its psychic stimulating effect, *i. e.*,  $\frac{1}{12}$  to  $\frac{1}{6}$  grain (5 to 10 mg.) by mouth, had no significant effect on the cardiovascular dynamics. The effects of epinephrine, *viz.*, marked tachycardia, increase in cardiac output, and acceleration of circulation time with only moderate transitory elevation of systolic blood-pressure and no rise or even a fall in diastolic blood-pressure, are quite different from those of benzedrine and paredrine; furthermore, epinephrine tends to precipitate ventricular arrhythmias, which neither

benzedrine nor paredrine has been observed to do.

The prolonged pressor action of paredrine, with no increase of cardiac output and no psychic stimulating effect, suggests that it may be useful in the treatment of certain types of vascular collapse, especially where stimulation of the myocardium may be undesirable. Favorable results from the use of paredrine have been observed in orthostatic hypotension, and in correction of the fall in blood-pressure during spinal anesthesia (Altschule and S. Gilman).<sup>29</sup> It must be borne in mind, however, that the effects of paredrine on the cardiovascular dynamics in all clinical conditions are not necessarily the same as those observed in this investigation on persons with normal cardiovascular systems, and, therefore, the widespread use of the drug should await further studies.

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## ELECTROCARDIOGRAPHY

**Prediction of Differences Between Precordial Leads CR, CL and CF, Based on Limb Lead Findings**—In taking precordial electrocardiographic leads opinion has been divided as to where to place the peripheral electrode. The leads CR (precordium, right arm), CL (precordium, left arm), and CF (precordium, left leg) differ from each other (in some cases quite markedly, as shown in Fig. 7). In a given case 1 peripheral electrode arrangement may produce the "most normal" deflection, whereas another will give rise to the "most abnormal." The recent observation of Wolferth and Wood<sup>30</sup> that if the size and direction of a certain electrocardiographic wave in 2 of the 3 limb leads are known, its algebraic relations in the precordial leads CR, CL and CF can be predicted, however, has thrown considerable light on the subject.

The fundamental principle which governs the predictions is inherent in Einthoven's equation, *i. e.*,  $\text{Lead I} + \text{Lead III} = \text{Lead II}$ , as are the equations published by the Committee of the

Wolferth and Wood. For the sake of readily designating each of the 2 electrodes of a given lead, the name "*terminal A*" is given to the right arm connection in Leads I and II, and to the

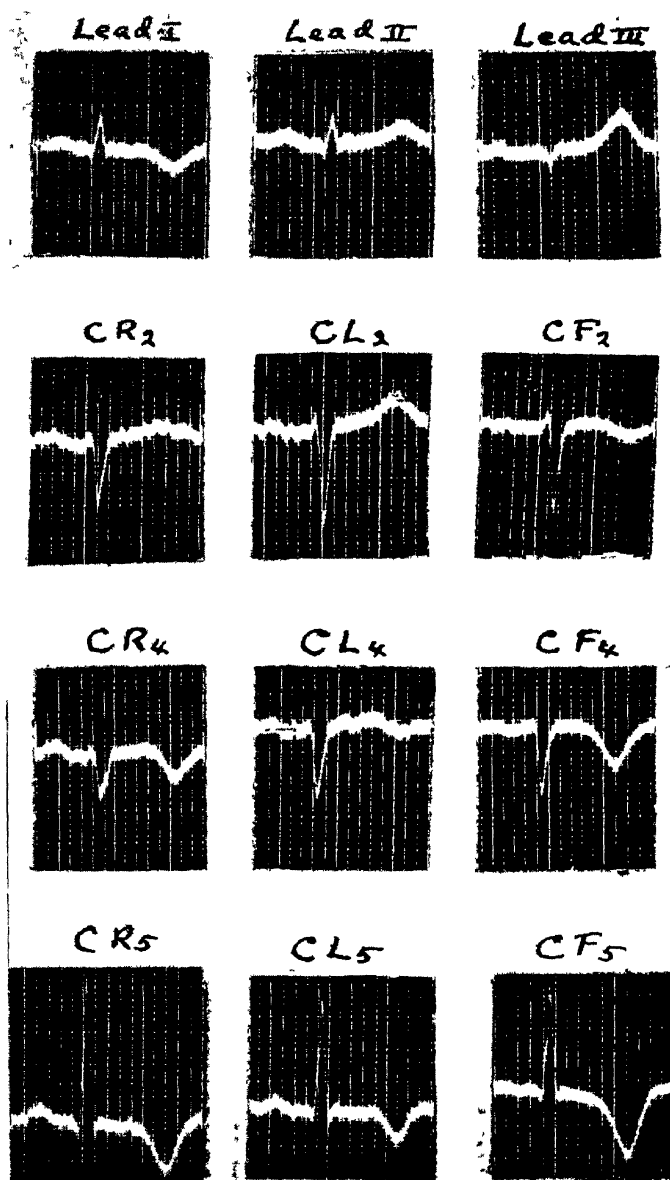


Fig 7—Electrocardiogram showing marked differences between T-waves in 3 precordial leads, CR, CL and CF, which are predictable from size and direction of T in limb leads (see Table III, Ex. 8). Details of method of prediction are described in text. (Wolferth and Wood: Am. Heart J.)

American Heart Association for the Standardization of Precordial Leads.<sup>31</sup>

In presenting the method of prediction, certain technical features of the electrocardiograph are reviewed by

left arm connection in Lead III; and the name "*terminal B*" is given to the left arm connection in Lead I, and to the left leg connection in Leads II and III. In precordial leads, as now taken, the



peripheral electrode is connected to "terminal A," and the precordial electrode to "terminal B." "The electrocardiograph is so constructed that, if terminal A is connected to the negative pole of a battery and terminal B to its positive pole, an upward deflection of the string shadow will be produced. It follows, then, that an upright wave in any standard electrocardiographic lead signifies that terminal B is connected to a point of higher potential than terminal A during the inscription of that wave. An inverted wave, moreover, signifies just the reverse, *i. e.*, that terminal A is connected to a point of higher potential than terminal B. When the string shadow is on the base line, terminals A and B are connected to points of equal potential. Just as the direction of a wave indicates which terminal (A or B) has the higher potential, so the amplitude of the wave indicates the potential difference between them. Thus, when the instrument is standardized in the usual way, a wave of plus 2 mm. in a given lead shows that, at the time of the peak of that wave, the potential of terminal B was 0.2 millivolt higher than that of terminal A."

According to Einthoven's law, if the size of any deflection in Lead I is known, the algebraic difference between that deflection in Leads II and III can be predicted. "For example, if  $T_1$  equals plus 2 mm.,  $T_2$  and  $T_3$  must differ by 2 mm. . . . An upright  $T_1$  signifies that the right arm is a point of lower potential than the left arm during T-wave inscription. Therefore, if leads are taken from the right arm and from the left arm to a third point, such as the left leg, using the third point as terminal B in both, the lead using the point of lower potential (right arm) as terminal A, *i. e.*, Lead II, will have a more positive T-wave than the lead using the point of higher poten-

tial (left arm) as terminal A, *i. e.*, Lead III. Consequently, when  $T_1$  equals plus 2, it can be predicted that  $T_2$  will be 2 mm. more positive (or less negative) than  $T_3$  . . . this relationship between Leads I, II, and III holds good not only when electrodes are on the arms and the left leg, but when they are on any 3 areas of the body surface. . . . In other words, just as it is possible to predict the algebraic difference between a wave in Lead II and one in Lead III when one knows its size and direction in Lead I, so is it possible to predict the algebraic difference between a wave in CR and one in CL when one knows its size and direction in Lead I. Applying the same principle, it is possible to predict, from Lead II, the algebraic difference between a wave in CR and CF; and it is possible to predict, from Lead III, the algebraic difference between a wave in CL and CF."

In Fig. 7,  $T_1$  measures minus 3;  $T_2$ , plus 2; and  $T_3$ , plus 5. At the peak of the T-wave, Lead I shows that the potential of the right arm is 0.3 millivolt higher than that of the left arm; Lead II shows that the potential of the right arm is 0.2 millivolt lower than that of the left leg; and Lead III shows that the potential of the left arm is 0.5 millivolt lower than that of the left leg. In other words, *the left arm has the lowest potential—0.3 millivolt lower than the right arm, and 0.5 millivolt lower than the left leg; the left leg has the highest potential—0.2 millivolt higher than the right arm, and 0.5 millivolt higher than the left arm; and the potential of the right arm is intermediate—0.3 millivolt higher than the left arm, and 0.2 millivolt lower than the left leg.* Consequently, of the 3 precordial leads (CR, CL, and CF), *Lead CL, from the left arm (the point of lowest potential) to the precordium, will show the most posi-*

TABLE III








































Examples	Limb Leads			When Paired with a Precordial Electrode:—*		
	T-1	T-2	T-3	The most normal (most + or least -) T wave will be obtained using the point of lowest potential, i.e.;	The intermediate T wave will be obtained by using the	The most abnormal (most - or least +) T wave will be obtained using the point of highest potential, i.e.;
(1)	 2	 4	 2	R. arm 4	L. arm 2	L. leg 0
(2)	 1	 4	 3	R. arm 4	L. arm 3	L. leg 0
(3)	 4	 4	 0	R. arm 4		L. arm & L. leg 0
(4)	 4	 2	 -2	R. arm 4	L. leg 2	L. arm 0
(5)	 4	 0	 -4	R. arm & L. leg 4		L. arm 0
(6)	 3	 -1	 -4	L. leg 4	R. arm 3	L. arm 0
(7)	 0	 4	 4	R. arm & L. arm 4		L. leg 0
(8)	 -3	 1	 4	L. arm 4	R. arm 1	L. leg 0
(9)	 -4	 0	 4	L. arm 4		R. arm & L. leg 0
(10)	 -4	 -1	 3	L. arm 4	L. leg 1	R. arm 0
(11)	 -4	 -4	 0	L. arm & L. leg 4		R. arm 0
(12)	 -1	 -4	 -3	L. leg 4	L. arm 1	R. arm 0
(13)	 -2	 -4	 -2	L. leg 4	L. arm 2	R. arm 0

TABLE III—In order to illustrate prediction of quantitative, as well as qualitative, differences, arbitrary values have been given to limb lead T-waves, and an arbitrary value of zero has been assigned to the smallest precordial T-wave (right hand column) in each example. Size of T-wave in other 2 precordial leads has been calculated from these figures.

\* Polarity as suggested by the Committee of the American Heart Association for the Standardization of Precordial Leads, i.e., extremity electrode is electrode A; precordial electrode is electrode B. (Wolferth and Wood: Am. Heart J)

tive T-wave; it will be 3 mm. more positive than the T-wave in a lead from the right arm to the same point on the precordium (CR), and 5 mm. more positive than the T-wave in a lead from the left leg to the same point on the precordium (CF). Moreover, Lead CF, from the left leg (the point of highest potential) to the precordium, will show the most negative T-wave. T in CF will be 2 mm. less positive than T in CR, and 5 mm. less positive than in CL. Finally, CR will

show a T-wave intermediate between the other 2, i.e., 3 mm. less positive than CL, and 2 mm. more positive than CF. In this example, both from precordial position 2 and precordial position 4, the differences are great enough to make the wave upright in CL and inverted in CF.

In Table III are shown a number of limb lead patterns and the predicted differences between the T-wave in the 3 precordial leads (CR, CL, and CF) for each pattern. The accuracy of these

predictions was tested in 70 cases in order to be certain that the time element did not introduce too large an error. The results are most clear cut when T-waves and limb leads are large, *i. e.*, when, during T-wave inscription, potential differences between extremities are large. When T-waves in limb leads are small, the application of the principle may be obscured by small differences in

The principle underlying predictions of the relationships is applicable not only when the electrodes are placed on the 2 arms, the left leg and the precordium, but when they are placed on any 4 points on the body surface. In Fig. 8, the right arm electrode was applied just above the right nipple, the left arm electrode just above the left nipple, and the left leg electrode over the lower end

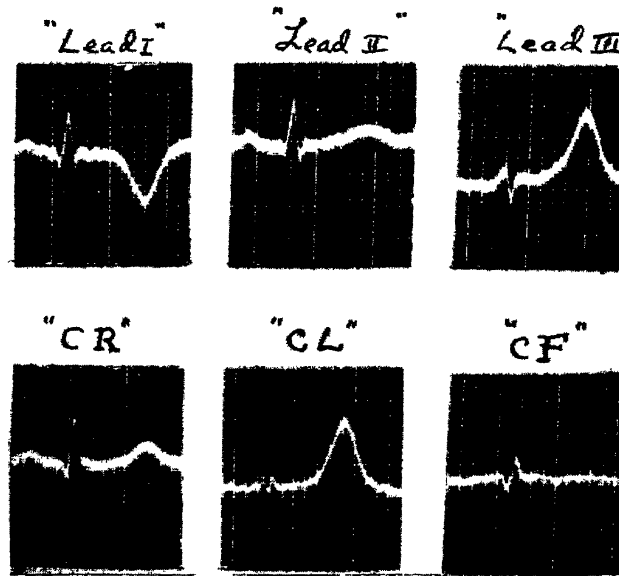


Fig 8—Electrocardiograms taken to show that method of prediction described in this paper holds when electrodes are placed on any 4 regions of body surface

Right arm electrode was placed just above right nipple. Left arm electrode was placed just above left nipple. Left leg electrode was placed over lower end of sternum. "Precordial electrode" was placed over gall-bladder.

Thus, "Lead I" is a lead from right nipple to left nipple, "Lead II" is from right nipple to lower sternum; "Lead III" is from left nipple to lower end of sternum; "CR" is from right nipple to gall-bladder region, "CL" is from left nipple to gall-bladder region; and "CF" is from lower end of sternum to gall-bladder region. T-wave pattern is that shown in Table III, Ex. 8. (Wolferth and Wood: *Am. Heart J.*)

string standardization, or by the phasic variation in the size of the T-wave so commonly seen in precordial leads. This method of prediction is applicable to the P-wave, the RS-T segment and the QRS complex. Since, however, during QRS inscription movements of the string often are very rapid, to make the prediction about the QRS complex it is necessary to have 2 leads recorded simultaneously in such a way as to bring out the time relations between them.

of the sternum. With these connections, the tracing taken on Lead I (right nipple to left nipple) has a T-wave of  $-8$  mm; the tracing taken on Lead II (right nipple to lower sternum) has a T-wave of  $+2$  mm; and the tracing taken on Lead III (left nipple to lower sternum) has a T-wave of  $+10$  mm. "These fundamental relationships might be stated in more general terms as follows: If one chooses any 3 points (A, B, and C) on the body surface, and takes

an electrocardiogram from A to B (Lead AB), from A to C (Lead AC), and from B to C (Lead BC), it can be predicted, from the size of T in any 2 of these 3 leads, which of the 3 points, when connected to a fourth point (P), will give the most positive T-wave, which will give the most negative T-wave, and which the intermediate T-wave. If Lead AB shows a positive T-wave, Lead AP will have a more positive T-wave than Lead BP. Moreover, the T-wave in AP will be more positive than the T-wave in BP by the amount of the size of the T-wave in Lead AB. If Lead AB shows an isoelectric T-wave, Leads AP and BP will have T-waves of equal size. If Lead AB shows a negative T-wave, Lead BP will have a more positive T-wave than Lead AP."

At the present time it is impossible to say which of the 3 leads, CR, CL, or CF, is best, but the following facts may have a bearing upon the decision: "(1) Patients with normal limb lead patterns (Table III, examples 1 to 4) will have the most positive T-wave in CR, and the least positive T-wave in CL or CF. (2) Patients with the usual limb lead pattern of acute pericarditis will have the most marked elevation of the RS-T interval in CR, and the least marked elevation in CF. (3) In cases of recent posterior infarction, CF will show the most marked RS-T interval depression, and CL will show the least. In cases of healed posterior infarction (Table III, examples 5 and 6), T-wave inversion will appear most frequently in CL, and least frequently in CF. (4) In cases of recent lateral infarction, CR would be most likely to show RS-T interval depression. (5) In cases of recent anterior infarction, in which the RS-T interval is elevated in Lead I, slightly depressed in Lead II, and definitely depressed in

Lead III, CF will show a greater RS-T interval elevation than CR or CL. In cases of healed anterior infarction (Table III, examples 2, 7, and 8), CF will be more likely to show T-wave inversion than CR or CL."

For the present the entire question of the choice of position for the peripheral electrode must remain unsettled. The authors are inclined toward the use of CF as a routine lead, since in cases of recent, and also of healed, infarction of the anterior surface of the left ventricle this lead is most likely to show an abnormality. Through routine use of CF leads only, there will be fewer "silent lesions"; and it is possible that there may be more "false positives," since normals would be most likely to show inverted T-waves in CF leads. Studies of control groups suggest, however, that when the precordial electrode is placed over the apex, an inverted T-wave in the CF lead rarely occurs when the heart is normal.

## PATENT DUCTUS ARTERIOSUS

**Mechanical Effects of Patent Ductus Arteriosus**—Studies of the circulation of patients with patent ductus arteriosus, by Eppinger and Burwell,<sup>32</sup> before and after ligation of the ductus by Gross (see SURGICAL TREATMENT), have set forth the following facts:

1. A stream of blood flows from the aorta to the pulmonary artery through the ductus during both systole and diastole (Fig. 9). This blood, shunted from the aorta without having gone to irrigate the periphery, returns through the lungs to the left side of the heart which it just left—thus serving no useful purpose. This is not a situation in which venous blood enters the arterial system but one in which arterial blood is entering the pulmonary system. These patients, there-

fore, are not cyanotic. From 45 to 75 per cent of the blood pumped out by the left ventricle into the aorta passes back through this short circuit into the pulmonary artery.

2. That portion of the blood in the aorta which is not shunted goes to the periphery and returns to the right ventricle. The right ventricle, therefore, has only 1 source of blood (*i. e.*, the peripheral circulation) while the left ventricle has 2 sources (*i. e.*, the blood from the right ventricle and the blood return-

2. Since both the left ventricle and the pulmonary artery are transmitting with each beat an increased volume of blood, they may be expected to show an increased pulsation.

3. Since the pulmonary artery receives blood from 2 sources, and since it has been seen at operation to have overflowed, the silhouette of this artery may exhibit unusual prominence.

4. Because of the increased flow of blood into them, the pulmonary vessels may show the signs of engorgement.

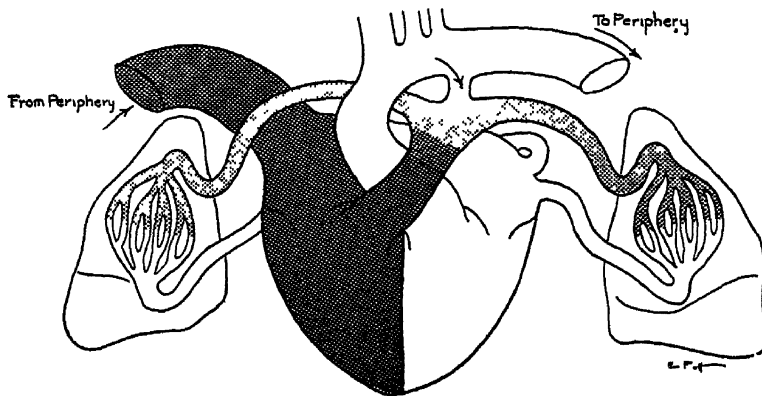


Fig. 9—Flow of blood in patient with patency of ductus arteriosus (Eppinger and Burwell: J. A. M. A.)

ing through the short circuit). In the cases studied the left ventricle had to pump from 2 to 4 times the amount of blood put out during the same time by the right ventricle.

3. The leakage of blood from the high pressure aorta to the lower pressure pulmonary artery is accompanied by a fall in the peripheral diastolic pressure and a slight rise in the pulmonary artery pressure. The actual measurements of the blood flow before and after operation are presented in Table IV.

The abnormal movement and distribution of blood in patent ductus arteriosus suggest the following signs which should be sought in *x-ray examination*:

1. The greatly increased output of the left ventricle indicates the possibility of the enlargement of this chamber.

5 The combination of increased inflow and engorgement may lead to increased pulsation of the pulmonary artery branches.

6. If a normal mitral valve is not wide enough to transmit this large amount of blood without an elevated left auricular pressure, there may be a visible dilatation of the left auricle. (It may be mentioned that 1 patient before operation showed a mid-diastolic apical murmur characteristic of mitral stenosis. Since ligation of the ductus this murmur has never been heard.)

The authors conclude that, on the whole, the x-ray signs are not sufficiently specific to supply final testimony concerning the diagnosis of patent ductus arteriosus. If, however, the relation of these x-ray signs to the dynamics of the

TABLE IV  
ACTUAL MEASUREMENTS OF BLOOD FLOW BEFORE AND AFTER LIGATION OF THE DUCTUS

Patient Number	Blood Flow Before Operation		Volume of Shunt, Liters	Percentage of Shunt	Blood Flow After Operation, Peripheral and Pulmonary, Liters
	Peripheral, Liters	Pulmonary, Liters			
2	5.9	25.4	19.5	77	5.1
3		19.1			6.2
5	4.8	8.7	3.9	45	3.3
6	6.0	14.1	8.1	57	6.3

circulation is understood, appropriate x-ray studies may suggest the diagnosis, contribute important confirmatory evidence, and bear important witness as to the effectiveness of therapy.

**Symptoms and Signs**—Correct diagnosis of patent ductus arteriosus can be made with a high degree of accuracy. The physical manifestations of the lesion may be entirely lacking in infancy and are apt to be confusing in the first 2 or 3 years of life, but are almost always typical after the fourth year. The murmur is continuous but accentuated during systole; in whole or in part it is widely transmitted over the precordium, to the axillae and to the back, but it has a maximum loudness in the second or third interspace to the left of the sternum. In contrast to the "blowing" or "harsh" murmur of pulmonary stenosis or coarctation of the aorta, it has an unmistakable rumbling quality, which has been described by the term "machinery murmur." The second pulmonic sound is almost always increased in intensity (if it is not overshadowed by the intense murmur), in contrast to the diminished or absent second sound in pulmonary stenosis. Some cases may present only a systolic murmur (the ductus presumably being small). A very coarse, precordial thrill, systolic in time or continuous with systolic accentuation, and most prominent over the pulmonic

region was present in each of the 10 cases, but some did not develop the thrill until the third or fourth year of life; and in cases in which the ductus is small a thrill may be absent. Usually the heart is slightly enlarged; the beat has accentuated vigor and a rate possibly somewhat increased. Since the left ventricle must pump a larger volume of blood *per* minute, and the right ventricle must pump against an elevated pressure in the pulmonary arteries, an additional load falls on both sides of the heart, and, therefore, the electrocardiogram usually shows no axis deviation. The blood-pressure shows no significant change in systolic level; but if the ductus is large, the diastolic figure is low, and a water-hammer pulse or a visible capillary pulsation may be detected on examination of the peripheral vascular system.

The physical development of the patient may be retarded, but this is not universally true. When patency of the ductus is the sole lesion, cyanosis is never observed unless the heart is failing and death is impending. If the ductus is small, no impairment of physical activity will be found, but if the fistula is large, a moderate but definite limitation of exercise is the rule; if it is widely patent, frank failure may supervene. In rare cases sudden collapse or death may occur, similar to that encountered with aortic valve insufficiency. The finding

of cardiac enlargement, prominence of the pulmonary artery, increased pulsation of the heart and great vessels, and pulmonary congestion on x-ray examination is in itself not enough to warrant a diagnosis of patent ductus arteriosus; however, it is valuable confirmatory evidence when evaluated with the clinical

physical growth, and heart-failure are frequent enough to warrant surgical attempts at closure of the ductus in selected cases with the hope of diminishing the incidence of the sequelae. In a report of surgical treatment of 10 cases of patent ductus arteriosus, Gross<sup>34</sup> states that operation should be advised

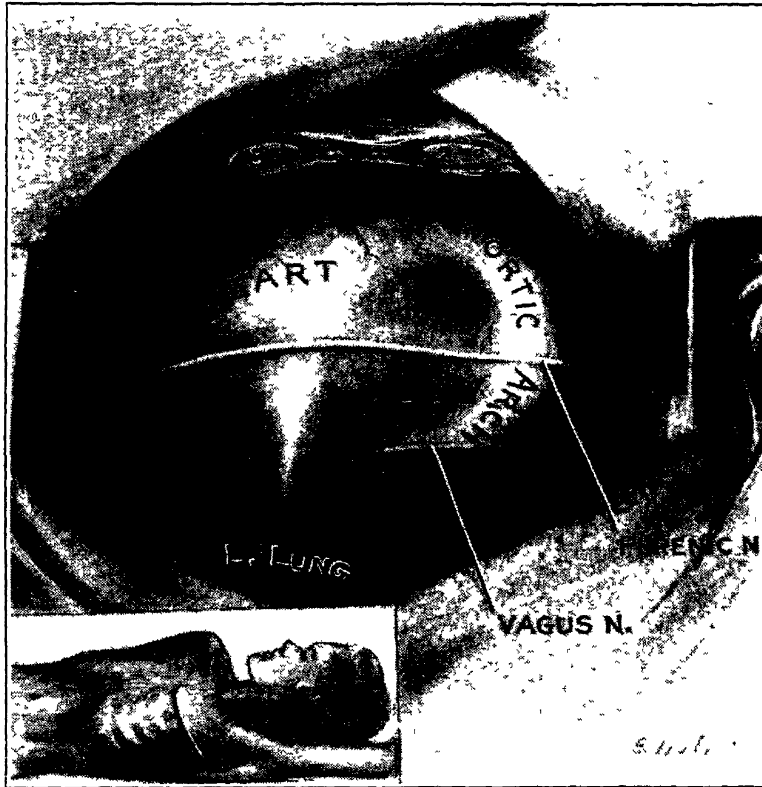


Fig. 10—Operative approach to ductus arteriosus. Insert shows position of patient and of cutaneous incision. Chest is entered through second interspace and second and third costal cartilages have been cut. Pleural covering of mediastinum will be opened along dotted line. (Gross: J. A. M. A.)

history, physical observations and electrocardiographic studies.

**Surgical Treatment**—Surgical ligation of patent ductus arteriosus, first reported by Gross and Hubbard,<sup>33</sup> constitutes a striking advance in medical history. The incidence of patent ductus arteriosus is not great; and it is difficult to state how frequently the abnormality gives rise to significant pathologic change. It is quite evident, however, that subacute bacterial endocarditis, retarded

only for carefully selected cases. With the procedure now employed (ligation), it is not felt that complete obliteration of the vessel can be accomplished in all cases; and, therefore, it is not believed that every patient should be operated on in the hope of preventing subacute bacteria endocarditis.

**Indications for Operation**—When the diagnosis of uncomplicated patent ductus arteriosus is reasonably certain, the dangers of the untreated abnormality

must be balanced against the possible hazards of operation. The fact that some people live a relatively long and active life, particularly if the ductus is small, should make the clinician cautious in advising surgical treatment. If the chances

by the diminution in peripheral flow resulting from the shortcircuiting of blood through the fistula, closure of the ductus is justified. This indication for operation is largely concerned with children from 5 or 6 years of age up to adoles-

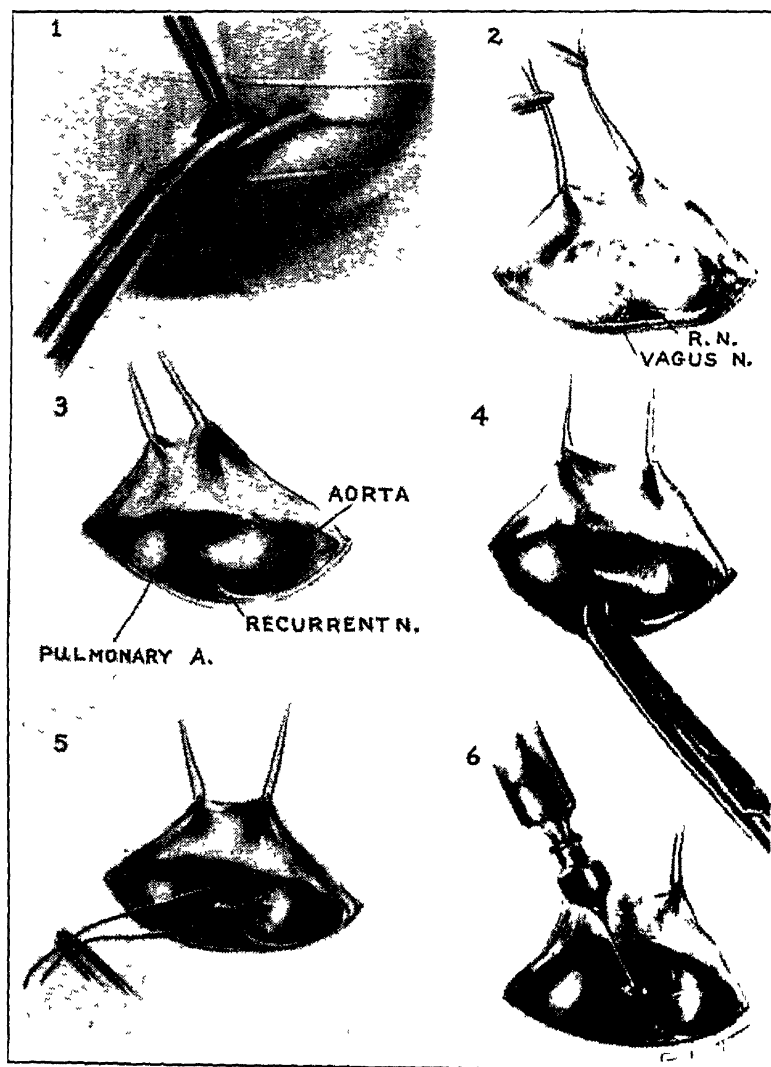


Fig. 11—Details of operative exposure of ductus: 1, Base of heart and great vessels; parietal pleura being opened along dotted line. 2, Presenting fat and areolar tissue dissected to isolate recurrent laryngeal nerve. 3, Ductus completely freed of overlying fat. 4, Posterior wall of ductus freed by blunt dissection. 5, Double ligatures in place, and one of them has been tied. 6, Both ligatures tied; sclerosing fluid being injected between them. (Gross: J. A. M. A.)

of developing important complications, however, appear to be relatively high, the risks of surgery can be taken with impunity. Criteria of selection of cases for surgery are as follows: When physical development is significantly retarded

cence. In some cases the deviation of blood by way of the shunt may be counterbalanced by an appreciable increase in the left ventricular output *per* minute; but in this accomplishment the heart may be so overworked that eventually myo-



cardial failure occurs. Physiologic studies showed the left ventricular output of some of the older patients in this group to be 2 or 3 times the expected normal. Myocardial failure rarely occurs before puberty; if ever it is to be a serious menace, it almost invariably manifests itself before the age of 30 years. The presence or history of cardiac failure in any form is a definite indication for operation; this includes any cardiac embarrassment, such as appreciable enlargement of the heart, undue increase in its rate and beat after mild exercise, and overactive cardiac impulse by physical or fluoroscopic examination, even though frank failure does not exist.

The question of whether the danger of a future *Streptococcus viridans* infection is a justification for operation is debatable. Theoretically, if the fistula could be closed off and the swirling of blood in the pulmonary artery be thereby abolished, the subsequent incidence of fatal bacterial infection would probably be reduced. Complete obliteration of the vessel can be accomplished by ligation in some cases, but there are others in which a tiny pinhole opening persists no matter how tightly the ligatures are applied. Ligation of a ductus can diminish greatly the mechanical burden of a heart and can improve the peripheral circulation, but at the same time a small opening can maintain some swirling of pulmonary artery blood and continue the danger of subacute bacterial endocarditis. It is believed, therefore, that, with the present operation, there is little justification for submitting individuals to surgery solely for the theoretical prevention of future endocardial or pulmonary artery infection. For the patient with a superimposed *Streptococcus viridans* infection which presumably will end fatally, closure of the ductus may diminish eddying of blood in the pulmonary ar-

tery, limit the formation of bacterial vegetations, and permit better treatment by chemotherapy. This optimistic view, however, must be discounted by the fact that a ductus or pulmonary artery which is the seat of bacterial vegetations is apt to be eroded and friable, and may rupture with surgical manipulation.

**Operative Technic**—The ductus can be adequately and safely brought into view by an approach through the left anterolateral chest wall (Fig. 10), traversing the left pleural cavity, temporarily collapsing the left lung, opening the parietal pleura of the mediastinum (Fig. 11), and then dissecting down between the great vessels. Great care and patience must be exercised in freeing and isolating the ductus. Heavy braided, waxed, silk ligatures were used in all cases, and this was supplemented in the more recent ones by injecting a sclerosing fluid between double ligatures. Following ligation of the ductus, the left lung is re-expanded with positive pressure, and the chest is closed. In 8 cases the anesthetic was *cyclopropane*, but in the other 2, *ether* in a closed system served quite well; in no case was an intratracheal tube used, since a tightly fitting face mask adequately permitted positive pressure expansion of the lung whenever necessary.

**Results of Operation**—Eight of the 10 surgically treated patients have shown a progressive and gratifying improvement; 1 patient died 2 weeks after operation from a *Staphylococcus aureus* infection, and 1 who proved to have a complicated cardiac abnormality has derived only slight benefit from operation. One patient, aged 11 years, has shown a gain of 22 lb. (10 kg.) in 18 months after the operation; and a significant increase in weight has occurred in 3 other cases in 4, 12 and 15 months, respectively, after operation. The 8 patients particularly benefited have shown a definite improvement in capacity for exercise. Several patients spontaneously have noticed an improved peripheral circulation, their feet and hands being warmer than pre-

vously during cold weather. A rise in diastolic blood-pressure was found in each case after operation.

## PERIPHERAL VASCULAR DISEASE

### Thrombophlebitis

**Rôle of Vasoconstriction in Production of Clinical Manifestations**—In recent clinical and experimental investigations, Ochsner and DeBakey<sup>35</sup> have demonstrated that many of the clinical manifestations of thrombophlebitis are due to vasospasm of the arterial and venous systems, and that a re-establishment of the normal exchange of intravascular and perivascular fluids can be produced by interruption of the vasoconstrictor impulses with procaine hydrochloride infiltration of the sympathetic ganglions.

"As a result of the vasoconstricting impulses initiated in the thrombosed segment there occur a number of factors which tend to increase the amount of perivascular fluid, *i. e.*, edema (Fig. 12). Venous spasm, in addition to the mechanical blockage of the involved segment of vein, results in a marked increase in intravenous pressure. This increase in venous pressure augments the filtration pressure and favors the increased transudation of vascular fluid into the perivascular spaces. Because of the associated arteriolar spasm and evidences of diminished vascularity there probably occurs a relative anoxia of the capillary endothelium, favoring increased permeability of this membrane and consequent increased transudation of vascular fluid into the perivascular spaces (Fig. 12). The reflex vasoconstriction of the arterioles and the increased venous pressure produce a marked diminution in the arteriolar pulsations which are so essential for the flow of lymph, as

shown by McMaster and Parsons (Parsons and McMaster<sup>36</sup>; McMaster and Parsons<sup>37</sup>). This results in a decrease in lymph flow and stagnation of tissue fluids. Because of the accumulation of proteins in the perivascular fluid a vicious circle is set up in that the osmotic pressure of the perivascular fluids ap-

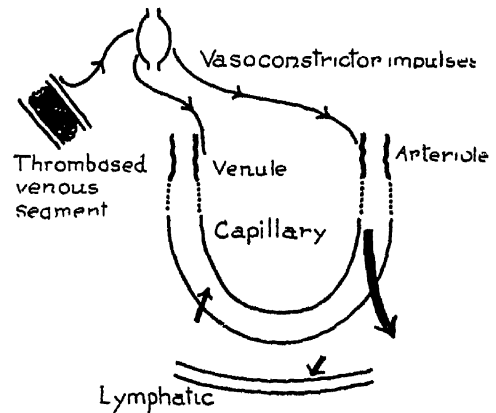


Fig. 12—Diagram of production of edema in thrombophlebitis. As shown by arrows, there is a greater amount of fluids leaving blood-vessels and entering tissues than that leaving tissues and entering blood and lymphatic vessels. Increased transudation of fluids from vascular system into perivascular spaces is due to several factors. As a result of vasoconstrictor impulses initiated in thrombosed venous segment there is produced a reflex vasospasm involving both arterial and venous elements of vascular tree. Thus, there occurs marked increase in venous pressure with consequent augmentation of filtration pressure and relative anoxia of capillary endothelium, both of which favor an increased transudation of vascular fluid into perivascular tissue. Marked diminution of peripheral pulsations consequent to vasospasm and increased venous pressure results in a decrease in lymph flow and stagnation of tissue fluids. (Ochsner and DeBakey: J. A. M. A.)

proaches that of the fluid within the vessels, tending to prevent the reabsorption of fluid from the perivascular spaces into the vascular tree."

By interrupting vasoconstrictor impulses with *procaine hydrochloride infiltration of the sympathetic ganglions* (Fig. 13), re-establishment of the normal exchange of intravascular and perivascular fluids has been accomplished both experimentally and clini-

cally In an experimental investigation DeBakey, Burch and Ochsner<sup>38</sup> found that ligation of the femoral vein in dogs brought about a marked diminution in volume pulsations of the corresponding foot and that a chemical irritant (sodium salicylate, 40 per cent) placed either in the lumen or in the perivascular tissue

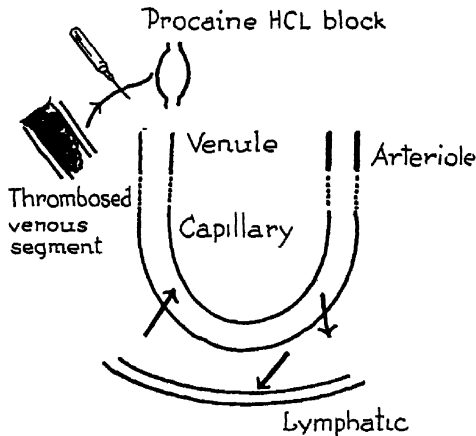


Fig. 13—Diagram of mechanism by which procaine hydrochloride block produces improvement in thrombophlebitic edema. Interruption of vasoconstrictor impulses results in decrease in venous pressure, increased vascularity and increased peripheral pulsations. Diminished venous pressure results in decreased filtration pressure and thus tends to prevent increased transudation of vascular fluid into perivascular spaces. Increased vascularity re-establishes normal oxygenation of vascular endothelium and permits return of normal permeability, which prohibits excessive transudation. Increased pulsations favor removal of perivascular fluids by increasing lymph flow. (Ochsner and DeBakey. J A M. A)

of an isolated segment of this vein produced further diminution in the pulse volume. Interruption of nerve pathways, however, by local infiltration of procaine hydrochloride around the site of the irritated segment or by resection of the lumbar sympathetic ganglions and chain abolished or prevented this effect. Similar observations have been made on patients with thrombophlebitis, who showed a definite decrease in the volume pulsations of the digits of the involved extremity; after procaine block

of the lumbar sympathetic nerves the volume pulsations returned to normal.

Of 15 cases with thrombophlebitis of the extremities, in 2 cases bilateral, treated by procaine block of the sympathetics, prompt and permanent relief of pain was effected in all instances; in one-half of the cases the edema completely subsided in 8 days, and in the remainder within 12 days; and 60 per cent of the patients were discharged from the hospital as cured within 8 days after the institution of therapy. In these cases there was considerable variation in the length of time between the onset of the thrombophlebitic process and the institution of therapy; the longest period was 28 days and the shortest 1 day. It was found best to make the injections every 24 to 48 hours as long as fever persisted. In the 17 thrombophlebitic processes, 6 had only 1 injection, 5 had 2 injections, 3 had 3 injections and 1 each had 4, 5 and 6 injections, respectively; thus, in 65 per cent of the cases relief was obtained by 2 injections or less.

In involvement of the lower extremity, the lumbar sympathetic ganglions were blocked with 1 per cent procaine hydrochloride, the posterior approach being employed, as described by the authors (Ochsner and DeBakey)<sup>39</sup> and as illustrated in Fig. 14. For the upper extremity the anterior approach to the stellate ganglion, as illustrated in Figs. 15 and 16, is preferred.

### Arteriosclerosis Obliterans

**Treatment**—That in recent years the trend in peripheral vascular disease has been toward conservative therapy as against radical surgery is pointed out by Wright.<sup>40</sup> Marked success has attended this trend in the treatment of thromboangiitis obliterans. The major amputation rate, which formerly averaged about 70 per cent, is now averaging from 3 to

10 per cent in several leading vascular clinics. On the other hand, however, arteriosclerosis obliterans has been less responsive to conservative therapy for a number of reasons:

1 We are dealing with older tissues with less resistance to infection and less capacity for regrowth

2 Many of these patients are seriously handicapped by diabetes mellitus, arterioscler-

capacity to the ischemic tissues in response to metabolic demands

4. Spasm plays a less important part in arteriosclerosis obliterans than in thromboangiitis obliterans, and hence therapy directed at the production of vasodilatation is, as would be expected, less effectual

In spite of these handicaps, definite improvement in the amputation rate has been achieved by the selective and con-

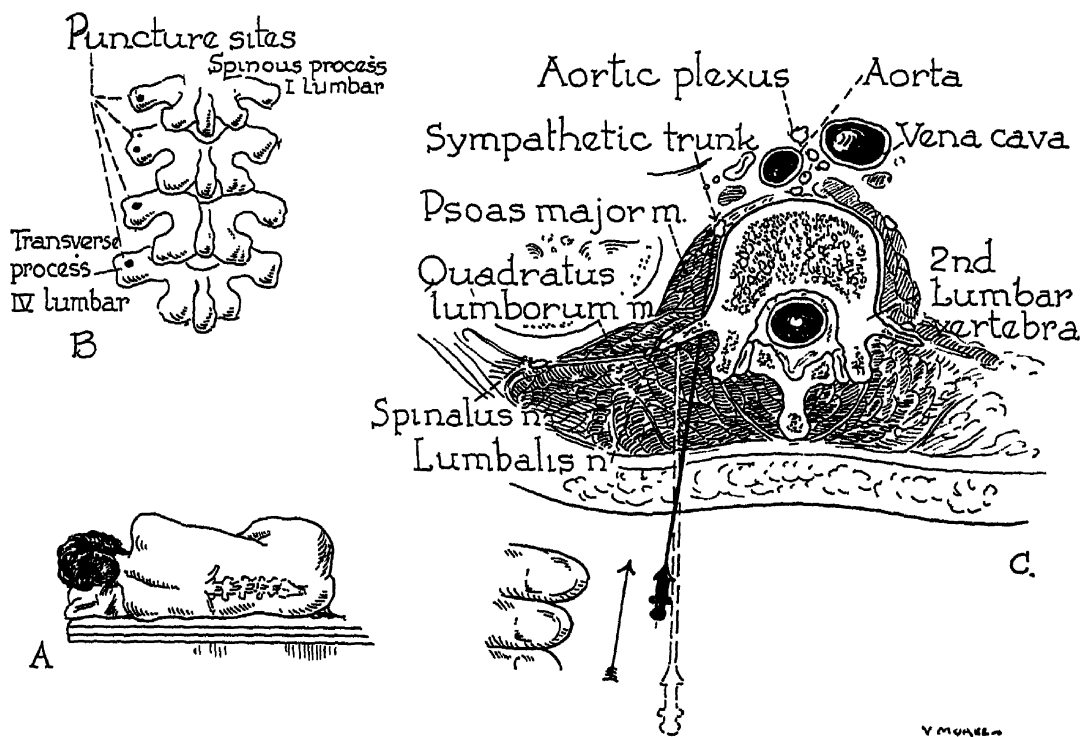


Fig. 14—Technic of lumbar sympathetic block in thrombophlebitis of lower extremities. A, Lateral recumbent position of patient. B, Cutaneous sites of puncture lie on a horizontal level with and  $2\frac{1}{2}$  fingerbreadths lateral to upper part of spinal processes of first 4 lumbar vertebrae. These puncture sites in the skin are immediately over transverse processes of respective vertebrae. C, Each needle is inserted vertically until transverse process of corresponding vertebra is reached as represented by dotted needle. Direction of needle is then changed slightly and inserted  $2\frac{1}{2}$  fingerbreadths beyond transverse process so that its point lies near anterolateral surface of body of vertebra where sympathetic chain lies. (Ochsner and DeBakey: Surgery)

otic renal disease, heart disease or other complications.

3. The point of blockage in arteriosclerosis obliterans is frequently, though not always, quite far proximal, thus blocking a large arterial trunk and reducing the possibilities for collateral circulation, whereas characteristically thromboangiitis obliterans begins by involving the minute distal vessels, very slowly extending proximally, giving the collateral vessels a better opportunity to establish their functional

considered use of the following important technics and medications:

1. **Rest of the involved extremities in a controlled temperature** of from  $88^{\circ}$  to  $94^{\circ}$  F. ( $31.1^{\circ}$  to  $34.4^{\circ}$  C.).

2. **Soaks and baths** at similar temperatures, using only mild solutions such as **saline**, **boric acid** or **azochloramide in triacetin** 1:500.

3. **Heat applied to the abdomen**, producing reflex vasodilatation.

4. **Postural exercises**, preferably passive, by means of the oscillating bed described by Sanders.

5 **Pressure-suction boots** in a few selected cases.

6 Alcohol in the form of *spirituous liquors by mouth*.

7. **Deproteinized** and other **pancreatic tissue extracts** by intramuscular injections.

8 Extreme general care in the **protection of the feet**.

pads, infra-red, diathermy and short wave machines

3 The use of strong antiseptics.

4 Meddlesome surgery in unskilled hands.

Of probable or possible value in the treatment of other vascular diseases, but of questionable value in the treatment of arteriosclerosis obliterans, in the writer's experience are:

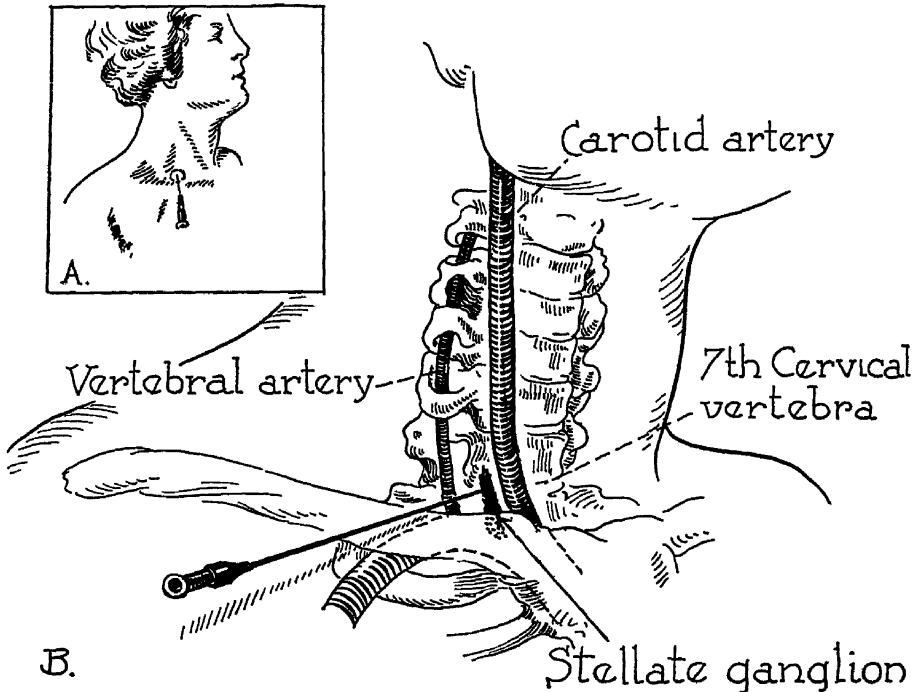


Fig 15—Technic of stellate ganglion block by anterior approach. *A*, Cutaneous site of puncture is 1 cm. medial to midpoint of clavicle and immediately over its upper border. *B*, Needle is introduced on a horizontal level with upper border of clavicle and directed posteriorly and medially at a 45° angle with midline. Point of needle impinges against anterolateral surface of body of seventh cervical vertebra at junction between seventh cervical and first thoracic vertebra. (Ochsner and DeBakey: Surgery)

9. Meticulous attention to any open lesions, using only correct technic in their care

10. Control of diabetes or other complications.

11. The judicious use of the **sulfanilamide compounds** in the presence of infections, selection being based on the organism present, if possible.

Of almost equal importance is the necessity of *avoiding*:

1. The use of tobacco.
2. The use of heat greater than 96° F. (35.6° C.), applied to the extremities—especially in the form of hot-water bottles, heat

1. Typhoid vaccine.

2. Saline or other solutions intravenously.

3. Intermittent venous hyperemia.

4. Mecholyl iontophoresis.

5. Sympathetic surgery.

6. Vasodilating drugs, nitrites and theobromine compounds.

7. Papaverine, except for its opiate effect.

Certain points should be carefully considered before amputation of an extremity is decided on:

1 The extent and spread of infection of the local lesion. Rapidly spreading, highly infected gangrenous areas sometimes demand amputation to prevent septic death. These are now subject to better control with the use of the sulfanilamide group.

2 The level of blockage of the major arterial trunk of the affected extremity, the amount of compensatory reserve and the collateral vessels active. These facts can be

amputation of the second leg. It is therefore of vital importance to be conservative if possible in such a case.

4 The age and general condition of the patient. It should be remembered that about 50 per cent of arteriosclerotic patients fail to learn to walk on an artificial limb after a mid-thigh amputation and that such a patient cannot usually be said to be living a full or useful life. Diabetes, when present, seriously com-

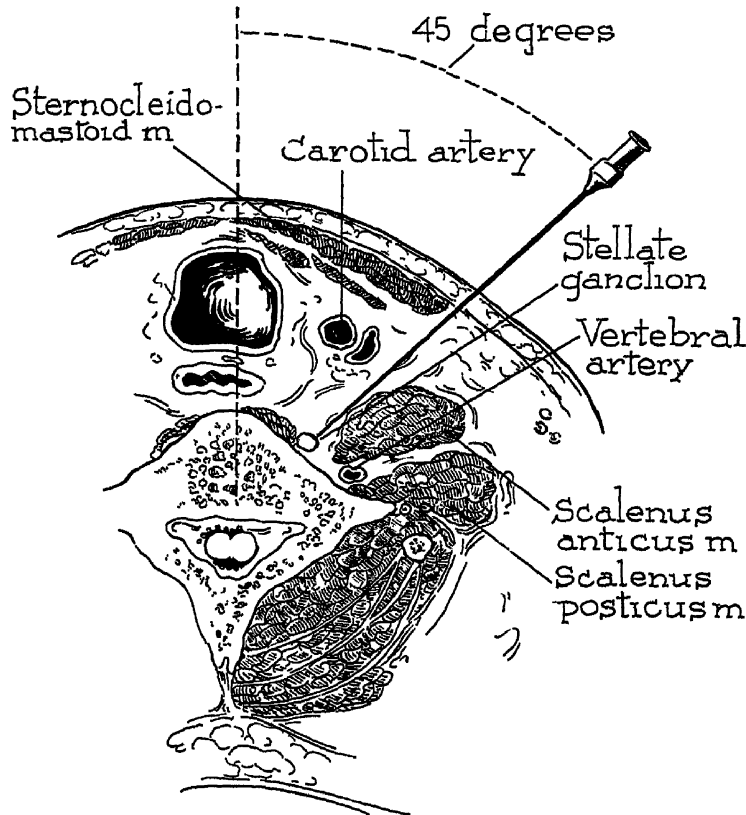


Fig 16—Diagrammatic drawing illustrating introduction of needle posteriorly and medially at a 45° angle with midline so that point of needle impinges against anterolateral surface of body of seventh cervical vertebra or at junction between seventh cervical and first thoracic vertebrae where stellate ganglion lies. (Ochsner and DeBaake Surgery)

ascertained by the use of the oscillometer, thermocouple readings with vasodilator tests, arteriographic studies, ergometric tests, histamine flare tests and other methods. Amputation should be high enough to avoid the need for secondary surgery.

3 The status of the remainder of the peripheral circulation. This is particularly important when 1 leg is involved. Examination frequently reveals that the circulation is actually poorer in the opposite leg, but, having escaped trauma, no open lesion has as yet appeared. Amputation of 1 leg in these cases is not infrequently followed shortly by the need for

plicates the entire picture, whether one wishes to be conservative or radical.

While it is easier to study the circulation of the extremities, information thus obtained may help one to understand similar processes occurring in less accessible blood vessels.

As stated by Wright, arteriosclerosis, the vastest of all medical problems of the future, remains the most neglected. The medical schools for the most part give

inadequate training in its study and care; and too frequently the practicing physician fails to recognize its manifestations until gangrene has occurred. Too few research workers have engaged in the study of arteriosclerosis, to a large extent because of lack of endowment. But "the question may well be raised as to whether we should justifiably bend our efforts toward the further prolongation of life unless we are prepared to insure that increasing age will bring happiness to the individual and avoid unbearable hardship on the community"

### **Development of Collateral Venous Circulation in Extremities**

The mode of development of venous collaterals after obstruction of the large veins of the extremities has been studied by Veal.<sup>41</sup> Occlusion of the main venous channels of an extremity produces changes in the local venous, arterial, lymphatic, and tissue fluid circulation; in the main, the alterations that occur depend upon the size of the veins involved, the level of occlusion, and the number of tributaries obstructed. In acute venous obstruction, particularly when caused by an inflammatory condition, there is an associated arterial spasm, which may be so marked as to simulate acute thrombosis or embolism. The end-results of impairment of the venous circulation of the extremities depend upon how much collateral circulation develops.

The first change that occurs after obstruction of a large venous trunk is an elevation of the local venous pressure. In a series of cases studied by Veal the elevation of the local venous pressure has ranged from 170 to 1400 mm. of saline. (The normal venous pressure in the arm at the level of the heart ranges up to 12 cm. of water; and in normal subjects fluid is filtered into the tissues of the forearm when the venous pressure

exceeds 15 cm. of water.) The collateral channels developed on occlusion of the large veins may be adequate only when the extremity is at rest and at the level of the heart; with prolonged exercise, or when the limb is allowed to hang in a dependent position for a long period, edema reappears. The swelling occurring after active exercise is a result of the tremendous increase in the volume of blood flow to the extremity and the fact that the venous outflow is not able to keep pace with the intake. Following the rise of venous pressure and the development of the edema, the lymphatic vessels are dilated, the valves become incompetent, and the lymph circulation becomes quite sluggish or ceases entirely.

After obstruction of a main venous trunk, the first venous structural change is dilatation of the vessel distal to the point of occlusion, with consequent failure of the valves to close completely, and the shunting of blood through the communicating veins into the more superficial companion trunks, such as the cephalic when the axillary and the subclavian veins are occluded (Figs. 17 and 18), and the great saphenous when the femoral and iliac veins are involved. These companion veins dilate, and their valves become incompetent. If this fails to compensate for the obstruction, there is a reversal of blood flow into the tributaries, and they become dilated, tortuous, and elongated; their branches, in turn, become enlarged, and there is a reversal of flow into these small veins. These new outlets form anastomoses with veins above the obstructed area. Often, long and tortuous courses are formed in an effort to provide an outlet for the venous blood which is under abnormally high pressure. In a few cases an outgrowth of small tufts of veins, budding from the tip of the obstructed vessel, has been observed.



Fig. 17—Normal venogram, made by injecting the basilic and cephalic simultaneously with a 2-way syringe. Note intact valves and absence of collaterals and tributaries. (Veal: Am Heart J.)



Fig. 18—Complete obstruction of basilic, axillary and subclavian veins. Tremendous development of collateral vessels over shoulder, upper chest and neck. Note tortuous, irregular course and distribution of collaterals. (Veal: Am. Heart J.)



As long as the superficial veins are allowed to remain open, there is little tendency to form new, deep connections or anastomoses in the deeper layers of the extremities because of the relatively greater tissue pressure therein; in fact, deep veins when obstructed have a tendency to grow much smaller as the collaterals develop into the main channels

arterial spasm by preventing the loss of heat from the extremity. It should be worn continuously for several months, until deep collaterals sufficient to compensate for the obstruction have been developed. The patient may be allowed out of bed as soon as the exciting cause of the thrombophlebitis will permit. By protecting the superficial venous circula-

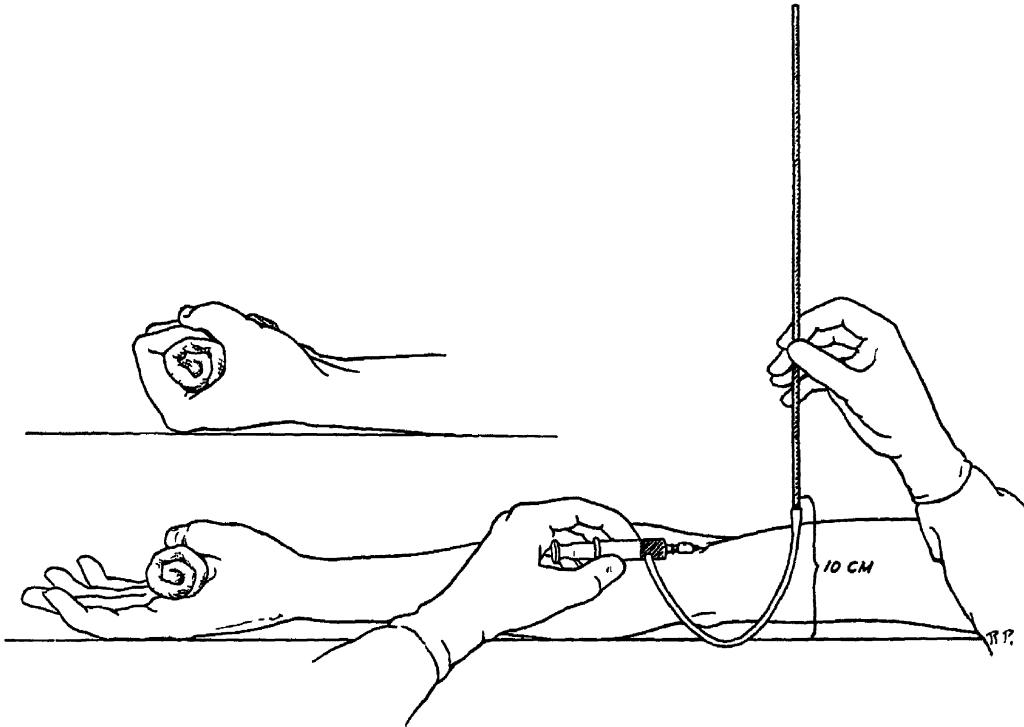


Fig 19—Apparatus and “exercise test” for studying antecubital venous pressure.  
(Veal and Hussey. *Am Heart J*)

This feature is very important because the superficial vessels depend to a great extent on muscular action to propel the blood forward; it is particularly true when the valves are incompetent and the limb is dependent. In an attempt to bring about the formation of deep collateral vessels after femorotibial thrombosis, encouraging results have been attained by obliterating the superficial veins immediately by the application of an *Unna's boot* from the toes to the hip. The boot tends to relieve the pain and lessen the edema; also it diminishes the

tion and encouraging the formation of deep collaterals, there is hope that the late sequelae of thrombophlebitis may be prevented.

### Venous Obstruction in Upper and Lower Extremities

“Exercise Tests” in Connection with Venous Pressure Measurements—Methods of measuring “general” or “local” venous pressure in the antecubital vein and “local” venous pressure in the popliteal vein during exercise have been described by Veal and Hussey.<sup>42</sup>

The apparatus used (Fig. 19) consisted of a 19-gauge needle and a 2 cc. syringe with a side-arm to which a calibrated glass measuring tube of 4 mm. bore is connected by means of rubber tubing; the other end of the glass tube is connected to a glass reservoir containing physiologic salt solution. With the arm abducted to an angle of about  $45^{\circ}$ , the needle is introduced into one of the veins of the antecubital fossa; and the plunger of the syringe is drawn back, allowing saline to run through the side-arm into the syringe, and thence into the vein. The reservoir is then detached from the apparatus, and the zero point of the calibrated tube is placed 10 cm. above the skin of the patient's back, which reference point has been shown by Lyons, Kennedy and Burwell<sup>43</sup> to be approximately level with the right auricle. With this technic, normal persons have a venous pressure of from 50 to 150 mm., which constitutes the basal venous pressure.

The usefulness of venous pressure measurements in the differentiation of edema caused by lymphatic obstruction from that caused by venous obstruction has been demonstrated in a study of cases of edema of the arm following radical mastectomy (Veal).<sup>44</sup> In certain cases of venous obstruction with established collateral circulation, inadequacy of the collateral circulation is shown by the appearance of edema following exercise. With the thought that measurement of venous pressure during exercise would indicate more actually the presence and degree of venous obstruction, *exercise tests* have been developed for use in the upper and lower extremities, respectively.

When the upper extremity is involved, the pressure in the antecubital vein is measured as usual, and then with the apparatus still in use, the patient is told

to close and open his hand, squeezing a roll of bandage tightly with each contraction and relaxing completely when the hand is open (Fig 19). This is continued for 1 minute, during which the patient usually will have clenched his fist from 30 to 40 times. It is important to have the patient restrict his exertion to the arm and to breathe regularly and evenly. If the venous pressure is so high that it cannot be recorded conveniently with the saline manometer, a mercury manometer can be substituted by means of a 3-way stopcock. In normal subjects a rise of more than 10 mm. of saline has not been observed, and at the conclusion of the exercise the pressure returns very promptly to, or slightly below, the basal level. In congestive heart-failure the venous pressure may be initially high, but the effect of the exercise test is the same as in normal persons. In cases of local obstruction of the axillary or subclavian vein, however, the venous pressure rises steadily during the exercise test, whether or not it is initially high, and it may reach a peak within the usual 1-minute period of exercise, or may not attain its maximum level until the exercise is continued for several minutes, or even longer. In every case of this type the rise of venous pressure has exceeded 50 mm. of saline (in 1 case the rise was 962 mm.); and on completion of the test the fall in pressure has been slower than in normal subjects, at times not reaching the initial level for several minutes.

Measurement of the femoral venous pressure is made with the same apparatus and technic as used for the upper extremity, except that a tourniquet is not needed. The needle is introduced through the skin into the femoral vein at a point about 1 inch distal to the inguinal ligament, just medial to the femoral artery. This method has found

practically no application in the study and diagnosis of localized venous obstruction in the lower extremity. The manifestations of obstruction of the iliac and femoral veins are often clear-cut and easily recognized. It may be difficult to be sure whether or not slight venous ob-

tions may not be altered by partial obstruction of the veins. Moreover, measuring the venous pressure in the leg or thigh while the patient is standing is usually not helpful in the diagnosis of venous obstruction because such pressures vary widely in normal persons,

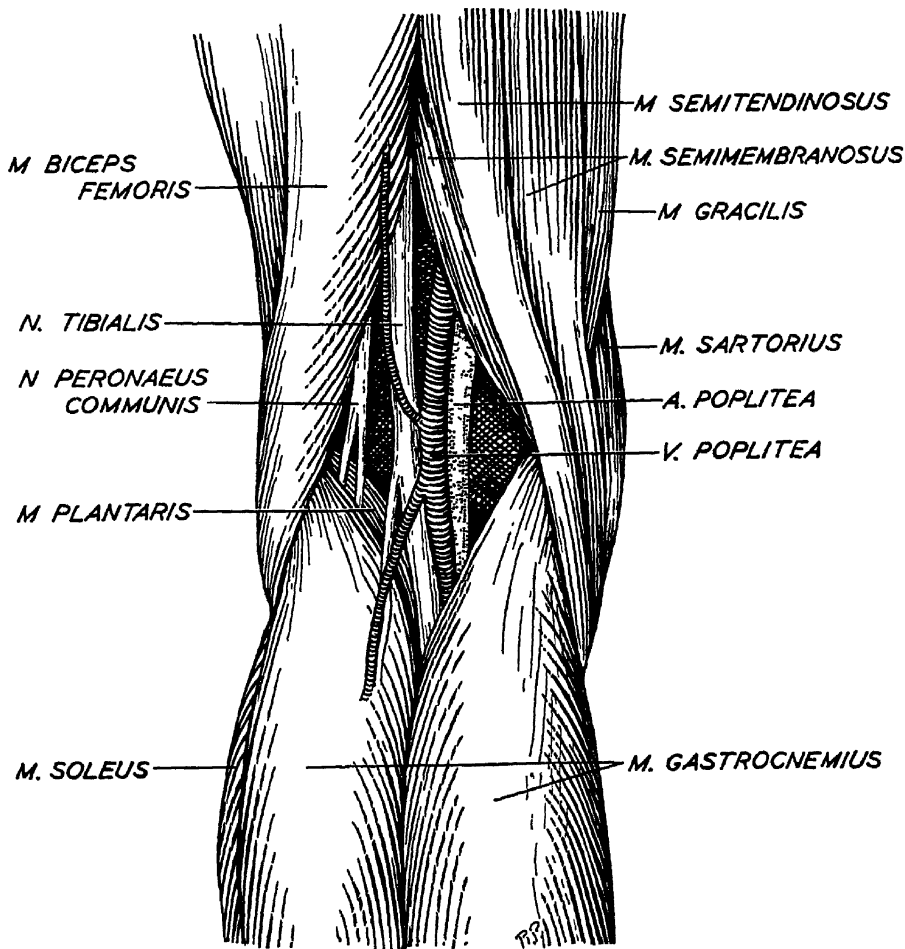


Fig 20—Anatomic relations of popliteal vein.  
(Veal and Hussey: Am. Heart J.)

struction is present, however, especially when clinical evidence of phlebitis or venous collateral circulation is lacking. In such cases measurement of the pressure in the femoral vein, or in one of the superficial veins of the leg, with the patient supine, may be of no assistance, and the results may even be misleading. Just as in the upper extremity, the venous pressure under relatively basal condi-

and only the "local" venous pressure can be measured in this way. A record of the changes which take place in the "local" venous pressure of the lower extremity during exercise in the upright position, obtained by using the popliteal vein, is useful, however, in the detection of venous obstruction.

The popliteal vein lies superficial to the popliteal artery and medial to the

The apparatus used (Fig. 19) consisted of a 19-gauge needle and a 2 cc. syringe with a side-arm to which a calibrated glass measuring tube of 4 mm. bore is connected by means of rubber tubing; the other end of the glass tube is connected to a glass reservoir containing physiologic salt solution. With the arm abducted to an angle of about  $45^{\circ}$ , the needle is introduced into one of the veins of the antecubital fossa; and the plunger of the syringe is drawn back, allowing saline to run through the side-arm into the syringe, and thence into the vein. The reservoir is then detached from the apparatus, and the zero point of the calibrated tube is placed 10 cm. above the skin of the patient's back, which reference point has been shown by Lyons, Kennedy and Burwell<sup>43</sup> to be approximately level with the right auricle. With this technic, normal persons have a venous pressure of from 50 to 150 mm., which constitutes the basal venous pressure.

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the column of mercury will fluctuate slightly, rising each time the patient moves up on his toes and falling when he lowers himself; the average range of this fluctuation is about 4 mm. above and below the initial pressure.

The study reveals that "exercise tests" are of particular value in connection with measurement of the venous pressure in cases of local venous obstruction in which the venous pressure is normal during rest and high only during exertion. The tests are apparently sensitive enough to detect venous obstruction when other signs are lacking. They are useful in distinguishing between various types of peripheral edema; and the positive response to the test in cases of chronic cardiac compression and compression of the superior vena cava by mediastinal tumors, or other lesions, renders it of value in the differentiation of these conditions from heart-failure.

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## PREGNANCY AND HEART DISEASE

**Cardiac Changes**—To ascertain the cardiac changes which may result from the gravid state, 73 apparently normal patients were followed through pregnancy by Sodeman.<sup>45</sup> The findings were grouped, as follows: (1) Physiologic changes, including so-called "gestatory heart disease"; (2) changes dependent upon toxemia and nephritis; and (3) post-partum heart-failure.

During pregnancy the enlarging uterus and its contents require nourishment and increase circulatory demands; new endocrine relationships appear; metabolic processes are accelerated; and cardiac displacement takes place, with an increase in the cardiac dullness to percussion and an increase in the transverse diameter on radiologic examination. In the latter half of pregnancy the

cardiac output is increased as much as 50 per cent above normal; and oxygen consumption, velocity of blood flow, and blood volume are increased. These changes have been explained as the result of an arteriovenous communication in the placenta, and from obstruction to venous return by the enlarged uterus.<sup>46</sup> But mere anatomic readjustments may be responsible, in part, for changes in the pulmonary second sound and edema of the ankles. The latter not infrequently is the result of interference with the return of blood from the lower extremities caused by pressure of the enlarging uterus.

**Physiologic Changes** — Thirty-one of the 73 patients developed palpitation or dyspnea, or both, of sufficient severity to constitute a complaint; only 2 patients suffered from choking or "smothering" at night. Soft systolic murmurs were common, and at times were markedly affected by posture. In 30 instances, soft, short, transient, systolic murmurs were heard; and of the more constant systolic murmurs, 18 were both apical and basal, 6 were apical alone, and 8 were basal alone. Two of the 6 apical, and 3 of the basal, murmurs failed to disappear post partum (these murmurs were present, but less loud, when the patient was first seen in the first trimester, apparently having been present before pregnancy); in the remaining patients, the murmurs appeared in the second and third trimesters. One patient presented a high-pitched, blowing aortic diastolic murmur. Gallop rhythm was found in 8, and a definite accentuation of the pulmonary second sound in 31 patients. In 12 individuals the heart was definitely beyond the midclavicular line (in 10 of whom the presence of enlargement was confirmed by x-ray examination) In 4 patients tachycardia was recorded graphically at some time or another; in

The apparatus used (Fig. 19) consisted of a 19-gauge needle and a 2 cc. syringe with a side-arm to which a calibrated glass measuring tube of 4 mm. bore is connected by means of rubber tubing; the other end of the glass tube is connected to a glass reservoir containing physiologic salt solution. With the arm abducted to an angle of about  $45^{\circ}$ , the needle is introduced into one of the veins of the antecubital fossa; and the plunger of the syringe is drawn back, allowing saline to run through the side-arm into the syringe, and thence into the vein. The reservoir is then detached from the apparatus, and the zero point of the calibrated tube is placed 10 cm. above the skin of the patient's back, which reference point has been shown by Lyons, Kennedy and Burwell<sup>43</sup> to be approximately level with the right auricle. With this technic, normal persons have a venous pressure of from 50 to 150 mm., which constitutes the basal venous pressure.

The usefulness of venous pressure measurements in the differentiation of edema caused by lymphatic obstruction from that caused by venous obstruction has been demonstrated in a study of cases of edema of the arm following radical mastectomy (Veal).<sup>44</sup> In certain cases of venous obstruction with established collateral circulation, inadequacy of the collateral circulation is shown by the appearance of edema following exercise. With the thought that measurement of venous pressure during exercise would indicate more actually the presence and degree of venous obstruction, *exercise tests* have been developed for use in the upper and lower extremities, respectively.

When the upper extremity is involved, the pressure in the antecubital vein is measured as usual, and then with the apparatus still in use, the patient is told

to close and open his hand, squeezing a roll of bandage tightly with each contraction and relaxing completely when the hand is open (Fig 19). This is continued for 1 minute, during which the patient usually will have clenched his fist from 30 to 40 times. It is important to have the patient restrict his exertion to the arm and to breathe regularly and evenly. If the venous pressure is so high that it cannot be recorded conveniently with the saline manometer, a mercury manometer can be substituted by means of a 3-way stopcock. In normal subjects a rise of more than 10 mm. of saline has not been observed, and at the conclusion of the exercise the pressure returns very promptly to, or slightly below, the basal level. In congestive heart-failure the venous pressure may be initially high, but the effect of the exercise test is the same as in normal persons. In cases of local obstruction of the axillary or subclavian vein, however, the venous pressure rises steadily during the exercise test, whether or not it is initially high, and it may reach a peak within the usual 1-minute period of exercise, or may not attain its maximum level until the exercise is continued for several minutes, or even longer. In every case of this type the rise of venous pressure has exceeded 50 mm. of saline (in 1 case the rise was 962 mm.); and on completion of the test the fall in pressure has been slower than in normal subjects, at times not reaching the initial level for several minutes.

Measurement of the femoral venous pressure is made with the same apparatus and technic as used for the upper extremity, except that a tourniquet is not needed. The needle is introduced through the skin into the femoral vein at a point about 1 inch distal to the inguinal ligament, just medial to the femoral artery. This method has found

congestion, elevation of the diastolic pressure without a comparable rise in systolic pressure, marked peripheral edema, and changes in the electrocardiogram. In the experience at Charity Hospital, New Orleans, recovery is slow; the outcome usually has been good; no deaths have occurred. Other clinicians (Gouley, McMillan and Bellet), however, have reported post-mortem findings on 4 similar patients—revealing myocardial degeneration “differing from the lesions ordinarily associated with the current classification of heart disease.” In these patients nutritional deficiency is common. Changes in endocrine functions may be an etiological factor. Since the time when symptoms arise coincides with the period in which full exercise is resumed, the concomitant additional strain upon the heart might be of etiologic importance. Parity and obstetric complications do not appear to be of primary etiologic importance. Recovery is slow; rest in bed is essential. Digitalis and the other therapeutic measures usually effective in heart failure have been of doubtful benefit.

The cardiac manifestations of the *nephritic* group are quite similar to those of the *nonnephritic* group. In the *nephritic* group, however, although evidence of acute left ventricular failure has been found, right-sided heart-failure has not occurred; the edema has been interpreted as *nephritic* in origin. Also, in the *nephritic* group some evidence of sepsis in the first few days of the puerperium, often initiated by a distinct chill, has been presented. After the stage of sepsis, a latent period of from 14 to 21 days then is followed by signs of hemorrhagic nephritis, including significant hematuria, albuminuria, casts in the urine, and edema, in addition to vascular changes. Diastolic hypertension in the *nephritic* group has been as marked

as in the *nonnephritic* group, and often has been accompanied by symptoms of encephalopathy. Age, parity, and the type of delivery appear to have little to do with the disease.

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## RHEUMATIC HEART DISEASE

**Pathologic Study of Rheumatic Heart Disease with Analysis of 796 Cases**—In a study by Clawson<sup>49</sup> of 4254 cases in which death resulted from noncongenital heart disease, rheumatic heart disease (including all forms immediately or indirectly caused by rheumatic infection) was a common, but not the most frequent heart disease encountered. In 1598 (37.6 per cent) of the cases, the heart disease was infectious in origin (rheumatic, bacterial, syphilitic, toxic myocarditis). There were 796 cases (18.7 per cent) of rheumatic heart disease; it was responsible for less than one-third of the cases of noninfectious heart disease (hypertensive heart disease, coronary sclerosis, and the various types of *cor pulmonale*).

The cases of rheumatic heart disease were divided into 4 groups: Acute rheumatic endocarditis, 98 cases (12.31 per cent); recurrent rheumatic endocarditis, 76 cases (9.54 per cent); valve deformities, 586 cases (71.6 per cent); and adherent pericardium, 36 cases (4.52 per cent). The *first group* was characterized by the presence of verrucous vegetations on valves which by gross examination appeared not to have been thickened previously; on microscopic examination, however, some of the valves showed such well-developed blood-vessels that the possibility of a previous infection was suggested. Auricular endocardial involvement was practically as common in cases of acute rheumatic endocarditis as in bacterial endocarditis. The *second*

*group*, comprising cases of recurrent rheumatic endocarditis, was similar to the first except that the vegetations were on grossly thickened fibrous valves; and in many cases there was a history of repeated attacks of rheumatic fever. The *third group*, comprising cases of valvular deformities, caused the greatest number of deaths (73.5 per cent); in some cases the valves were completely healed, and some showed signs of lingering infection. The calcified, nodular, aortic valve deformity, which is regarded by Clawson as a rheumatic lesion, comprised 40 per cent of all the valve deformities. If it were not included among the rheumatic lesions, it would have to be concluded that rheumatic infection of the aortic valve is uncommon. In more than half of the cases in the small *fourth group*, comprising cases in which death appeared to have resulted primarily from an adherent pericardium, slight valvular deformities were present also.

The relative *incidence* of rheumatic heart disease in *males* and *females* was: males, 27 per thousand; females, 31 per thousand. The females died earlier than the males, probably due to the fact that the mitral is the valve most commonly involved in females. Males and females with the same valve lesions died in the same decades. With a mitral valve deformity in either sex, myocardial efficiency cannot be maintained as long as with an aortic valve lesion. Death from acute and recurrent rheumatic endocarditis occurred chiefly in the early decades. Death from incompletely or completely healed valvular deformities took place primarily in the middle decades, and from the calcific nodular aortic valve deformity in the later decades. The valves of the left side of the heart were involved in 99.8 per cent of the cases. Involvement of the valves of the right side was present in 5.6 per cent of the

cases; but in all but 1 instance there was also a lesion of 1 or both of the valves of the left side of the heart. In the males the aortic and mitral valves were involved with equal frequency; among the females aortic involvement was less common than mitral development. The predilection for the mitral valve in females is not understood, but it helps to explain why the calcified, nodular, aortic deformity is common in old men.

Vegetations begin on the side of the valve where the spongiosa layer, which contains most of the blood-vessels, is located, *i. e.*, on the ventricular surfaces of the aortic and pulmonic cusps, and on the auricular surfaces of the mitral and tricuspid valves. This suggests that the infection may be embolic in origin; but, in some cases, small vessels can be seen leading from the surface indentations, which would indicate that infection may occur directly from the blood stream. Valves which were thickened and scarred from repeated attacks of proliferative inflammation, showed a marked tendency to become calcified. Proliferative inflammation, of a nodular (Aschoff nodule) or diffuse type, was usually present, and at times resulted in periarterial scarring. Such inflammation, although common, was not always present in cases of acute or healed rheumatic heart disease; it was more common during the acute stage. The stigmas of rheumatic inflammation were practically as common in the valve and myocardium in the cases of calcified, nodular, aortic valve deformities as in those with mitral valve deformities.

Cardiac hypertrophy was present in most of the cases; it was most marked in aortic valve involvement, and less pronounced when mitral lesions only were present. More hypertrophy was found among the males, apparently because



aortic lesions are commoner among males than females. Gross areas of fibrosis were rarely seen in cases of rheumatic heart disease, and with a few exceptions, the coronary arteries were relatively free from severe sclerosis. There was no indication that rheumatic infection bears any causal relation to coronary sclerosis. Pericarditis, either acute or in the form of adherent pericardium, was not a constant accompaniment of acute or recurrent rheumatic endocarditis; it was no commoner than in subacute bacterial endocarditis, and therefore cannot be used clinically in the differential diagnosis of acute rheumatic and subacute bacterial endocarditis. Death rarely resulted from the effects of an adherent pericardium alone.

Little evidence for or against any of the theories concerning the nature of the infectious agent in rheumatic heart disease was discovered. The type of inflammatory reaction within the valve was very similar to that which occurs in frank, streptococcic, subacute bacterial endocarditis—which fact might be regarded as evidence in favor of the streptococcic theory of the etiology of rheumatic fever. The fact that the inflammatory reaction is a “proliferative” one does not definitely support the virus theory. It is even questionable whether the Aschoff nodule, which varies so decidedly in structure, and is by no means constantly present in cases of rheumatic heart disease, is sufficiently characteristic to justify the suspicion that it is caused by a specific infectious agent.

Several facts of clinical value emerge from the analysis of the 796 cases of rheumatic heart disease. Rheumatic heart disease causes slightly less than 20 per cent of all deaths from noncongenital cardiac disease, which is nearly twice the number caused by bacterial endocarditis, and nearly 3 times as many as

result from heart disease secondary to syphilitic aortitis. As a rule, patients with acute rheumatic endocarditis die, not during an acute attack, but later, from the effects of valvular stenosis and insufficiency. Males and females in about equal numbers are affected by rheumatic heart disease; but the males tend to live longer than the females. The aortic and mitral valves are involved with equal frequency in males; but mitral valve involvement greatly predominates in females. Both males and females survive longer with an aortic than with a mitral lesion. Tricuspid and pulmonic lesions, especially healed deformities, rarely occur without an associated aortic or mitral lesion. All non-syphilitic aortic valvular deformities which lead to cardiac failure appear to be rheumatic in origin.

**Valvular Calcifications in Rheumatic and in Nonrheumatic Heart Disease**—One hundred and forty-eight consecutive cases of fatal rheumatic heart disease and 125 consecutive cases of nonrheumatic heart disease have been reviewed by Epstein<sup>50</sup> with regard to (1) the incidence and distribution of calcifications of the aortic and mitral valves, (2) the interrelationship, if any, between the presence of valvular calcifications and the duration of heart disease and symptoms of heart-failure, (3) the coincidence of valvular calcifications and pericarditis, disease of the coronary arteries, aortic calcification and electrocardiographic changes, and (4) the influence of valvular calcifications on the weight of the heart.

Slight and moderate calcifications in the mitral valve, found in 64 cases of rheumatic heart disease, were located most frequently in the leaflets. The smallest deposits were situated on the bodies of the leaflets or the endocardium of the left auricle adjacent to the insertion of

the leaflets; when the lesions were extensive the free margins were often involved. In 38 cases deposits were limited to the mitral valve; mitral stenosis or a double mitral lesion was present in each instance in this group. The degree of valvular deformity, however, did not necessarily parallel the degree of calcification. Pinpoint mitral ostia occurred in hearts with minimal calcifications, as well as in those which had far more extensive deposits; and tight mitral stenosis, with leaflets of cartilaginous density, was not uncommon in patients who had no valvular calcifications, particularly those in the younger age groups. Extension of the calcifications into the annulus of the mitral valve was uncommon. Calcifications limited to the aortic valve occurred in 16 of the cases of rheumatic heart disease; 8 others had calcifications of the mitral as well as of the aortic valve, and 2 patients had extensive trivalvular deposits, involving the mitral, aortic, and tricuspid valves. Twenty of these 26 patients were over 40 years of age. In patients under 30 years of age with rheumatic heart disease, calcifications of the aortic valve were accompanied by extensive changes and calcification in the mitral valve. In older patients the aortic valve lesions associated with the calcific deposits were usually less extensive than those in younger persons. Frequent association with lesions of mitral valve was found, but calcifications in mitral leaflets in such persons were not common. The electrocardiographic changes in the rheumatic group were those usually associated with active rheumatic heart disease and disease of the coronary arteries.

In the group of 125 patients with non-rheumatic (hypertensive and arteriosclerotic) heart disease, calcifications were present in the valves of 27 (16 males and 11 females), all over 50 years

of age. The mitral valve alone was involved in 9 instances; the aortic valve alone in 12; the mitral and aortic valves in 4; the mitral, aortic and tricuspid valves in 1; and the mitral, aortic and pulmonary valves in 1. In each of the 9 cases the calcifications of the mitral valve were limited to the annulus (7 being of advanced degree; 2, moderate). Concomitant valvular defects were uncommon in this group. That the auscultatory findings were within normal limits may indicate that the calcifications did not produce significant changes either in the anatomic function of the valve or in the heart sounds. Calcifications of the aortic valve in nonrheumatic heart disease were equally frequent in the leaflets and in the annulus; in some instances both structures were involved. Five of the 12 patients with calcifications limited to the aortic valve had valvular defects; 2 had double aortic lesions; 2, aortic insufficiency; and 1, aortic stenosis; the calcific deposits were "advanced" in 4 of the cases. Of the remaining 7 patients, 3 had extensive calcifications without valvular defects. Aortic valvular defects due to calcific deposits were relatively frequent, but, as a rule, were not as extensive as those seen in cases of rheumatic heart disease with calcification of the valves. Advanced calcifications of the aortic valve, however, were present in patients who had had neither clinically demonstrable defects of the aortic valve nor symptoms of heart-failure. The electrocardiographic changes were those resulting from disease of the coronary arteries. Auricular fibrillation and partial bundle-branch block were the most frequent arrhythmias. No changes which might be interpreted as indicative of calcifications of the aortic valve could be demonstrated.

The weights of the hearts with calcified valves were independent of the de-

gree of calcifications Disease of the coronary arteries and aortic arteriosclerosis with calcification were more frequent in the nonrheumatic than in the rheumatic group. Patients with rheumatic heart disease who had survived the age of 40 years, however, had calcific deposits similar in extent and distribution to those of patients with nonrheumatic heart disease. In view of the fact that the incidence of calcifications of the aortic valve was definitely greater in the rheumatic group after the age of 40 years, it is reasonable to assume that the same process might be responsible for the calcifications in the 2 groups. The possibility of calcification occurring on the site of an old rheumatic lesion, thereby speeding the disease process, deserves consideration. Pericarditis was more frequent in the rheumatic group, and, when present, may point to a rheumatic origin.

The presence of calcifications in the heart valves did not appreciably alter the prognosis, nor did there seem to be any relationship between the duration of symptoms of heart-failure or of known heart disease and the presence of calcareous deposits. The symptoms of heart-failure appeared to be related to the effect of the valvular deformity on the myocardium. And the degree of valvular deformity may be the same with or without calcareous deposits, which fact is borne out by the similarity in the incidence of heart-failure in patients with rheumatic heart disease and in those without valvular calcifications, as well as by the relatively low incidence of heart-failure in nonrheumatic heart disease with valvular calcifications.

#### **Pure Mitral Stenosis in Young Persons**

In a clinical study of 81 young patients with physical signs of so-called

pure mitral stenosis, Walsh, Bland and Jones<sup>51</sup> have concluded that a relatively mild form of rheumatic fever appears to favor the development of this particular lesion. In the majority of instances, the evolution of the physical signs prior to the establishment of this valvular deformity required 5 to 15 years. In the study the physical signs which characterized pure mitral stenosis were (1) a low-pitched (often coarse) murmur at or near the cardiac apex, which begins in mid or late diastole and ends with crescendo in (2) an abrupt, slapping first sound; a corresponding thrill and shock were commonly associated with the more advanced lesions, and accentuation of the pulmonary second sound was usually present. A considerable number of patients with undoubted mitral stenosis who, in addition to the physical signs mentioned, had a blowing systolic murmur at the apex, characteristic of associated mitral regurgitation, were excluded. The average age at which the initial rheumatic fever began in this special group was 9.3 years, which closely approximated the age of onset in 1700 children studied since 1920 at the House of the Good Samaritan in Boston. No patient beyond 21 years of age at the onset of rheumatic fever was included.

In 48 of the 81 patients the changing physical signs in the heart prior to the stage of pure mitral stenosis were observed; in the remaining 33 patients the signs were already established when the patients were first seen. As shown in Table V, in relatively few instances (5 patients) did pure mitral stenosis become established in the first five-year period; the earliest occurrence was 3 years after the initial attack of rheumatic fever. In the majority of the patients (27), it developed during the second 5-year period. But in 14 individuals the

TABLE V  
DEVELOPMENT OF PURE MITRAL STENOSIS (48 PATIENTS)

Original Status	Number of Patients					
		Period from Onset of Rheumatic Fever to Established Mitral Stenosis (Years)				
		1-5	6-10	11-15	16-20	20-24
Group 1: Rheumatic heart disease ..	27					
(1) Mitral involvement (regurgitation) .	5		1	2	1	1
(2) Mitral involvement (regurgitation and ? stenosis) .	15	1	10	3	1	
(3) Mitral involvement (? stenosis) . .	4	1	1	1		1
(4) Aortic regurgitation (slight) . . .	3	1	2			
Group 2: Potential rheumatic heart disease	21	2	13	2	4	
Totals . . . . .	48	5	27	8	6	2

characteristic signs did not become established until the third 5-year period after the original rheumatic fever; and in 2 others it was established more than 20 years after the original illness. In 17 patients the initial illness was manifested by uncomplicated chorea (which the authors consider a manifestation of mild rheumatic fever); and the remaining 64 patients (with 1 exception) were also considered to have a mild form of rheumatic fever. In 4 cases there was an absence of a recognizable illness prior to the appearance of heart disease; in 13, a period of poor health of obscure nature immediately preceding the appearance of heart disease; and in 46, in addition to poor health, either characteristic joint pains or chorea. Recrudescences occurred in 69 (85 per cent) of the 81 patients.

Recognizable involvement of the heart was present with the initial attack of rheumatic fever in only 57 per cent (60 of the patients), whereas with the larger group of 1700 patients an initial involvement of the heart occurred in approximately 70 per cent. The high percentage (73 per cent) of patients with no initial enlargement of the heart and the infre-

quency of even a moderate degree of enlargement for the remainder are striking. The subsequent failure of the heart to enlarge significantly in the majority of patients, in the presence of both recurring infection and developing stenosis, is an additional and important indication of the relative mildness of rheumatic fever. Fifty-three (65 per cent) of the total group of 81 patients are leading normal lives, while 13 (16 per cent) are slightly limited and 4 (5 per cent) are moderately limited by dyspnea on exertion. The remaining 11 patients (13 per cent) have died, which is in striking contrast to a death rate of approximately 24 per cent for a control group of 1000 young rheumatic patients of essentially the same age, followed for a comparable length of time (10 years).

In the light of the observations on younger patients in whom pure mitral stenosis has developed as a result of mild rheumatic fever, the unusually high percentage of older patients with a "negative" rheumatic history is more readily understood. That in many older patients pure mitral stenosis may appear insidiously and remain clinically silent for years is well known; not uncommonly,

the ultimate appearance of auricular fibrillation may direct attention for the first time to the heart, and less often the occurrence of hemoptysis, pulmonary infarction, acute pulmonary edema, or peripheral embolism leads to the discovery of previously unsuspected mitral stenosis. It is probable that the favorable course of the illness in the majority of these patients (both young and old) is to be accounted for by the mild rheumatic fever, which in turn favors the continued integrity of the myocardium.

### Subclinical Mitral Disease

The value of *x-ray examination* in the diagnosis of mitral stenosis, even in the absence of characteristic physical signs, is emphasized by Sosman.<sup>52</sup> Careful auscultation is the most widely used and the most accurate method of diagnosing mitral stenosis. But the typical auscultatory features of mitral stenosis may be absent or overlooked (*a*) in the early stages of the process, when the change in the diameter of the valve orifice is slight and the murmur absent or very faint, and (*b*) in the advanced stages of the process, particularly when there is heart-failure. (When great dilatation of the chambers is present, the velocity of the blood flow may be quite slow, and the murmur very faint or absent; but the murmur may reappear as the myocardial insufficiency disappears, which is particularly true when auricular fibrillation accompanies heart-failure).

In the great majority of the cases of mitral stenosis, x-ray examination will demonstrate dilatation of the left auricle, which is best seen in the right anterior oblique position and may be of sufficient degree to displace the esophagus posteriorly and sometimes to the patient's right. In the posteroanterior view the change in the cardiac contour may be less marked and less character-

istic; there may be only a straightening of the normally concave "waist" of the heart on the left border, a contour not typical of mitral disease. In the more advanced cases the left contour presents the double convexity of the dilated pulmonary artery and the tip of the dilated left auricle between the aortic knob and the left ventricular contour (Figs. 21, 22 and 23).



Fig 21—Case 2. Seven-foot film of heart showing general cardiac enlargement and double convexity in middle third of left cardiac contour suggesting mitral stenosis. (Sosman. J A M. A)

In the study of heart disease *fluoroscopic examination* is much more valuable than are x-ray films. The fluoroscopic examination of a patient with mitral valvular disease should reveal:

- "1. A straightening or a double convexity of the midportion of the left cardiac contour. 2. Dilatation of the left auricle posteriorly, best shown in the right anterior oblique position. The convex curve of the dilated auricle is located in the middle third of the cardiac shadow and may obscure the middle third of the posterior mediastinal space. 3. Widening of the base of the heart in the right anterior oblique view, due to the combination of enlarged pulmonary conus anteriorly and dilated left auricle posteriorly.

"Fluoroscopy may also show: 4. Displacement of the barium-filled esophagus posteriorly, with moderate to marked dilatation of the auricle, best shown during the expiratory phase but most reliable when also present during inspiration. 5. Dilatation of the pulmonary vessels at the lung roots due to stasis in the pulmonary circulation. These ves-



Fig. 22—Case 2. Right anterior oblique film showing marked dilatation of left auricle (arrows) projecting beyond anterior border of spine (Sosman J. A. M. A.)

sels do not pulsate as in Ayerza's disease and patent ductus arteriosus. They may be considerably dilated and congested without producing physical signs or symptoms. 6. Hypertrophy of the right ventricle, seen best in the exaggerated left anterior oblique view, which reveals a ledge or shoulder projecting anteriorly. 7. Narrowing of the precardiac space in the lateral view, with a greater amount of the heart in contact with the sternum than normal, and (8) a hypoplastic aortic knob, in cases in which the mitral stenosis was acquired in childhood. Marked dilatation of the pulmonary artery may partly obscure the aortic knob, making it seem hypoplastic by comparison. The real hypoplasia is thought to be due to a decreased volume of blood from the left

ventricle, in turn due to the mitral stenosis."

*Calcification* in the injured valve is found in a majority of cases of mitral stenosis at autopsy, but, unfortunately, is not visible fluoroscopically in more than 10 per cent of the patients during life, which fact is in striking contrast to aortic stenosis, in which calcium deposits large enough to be readily demonstrable under the fluoroscope are present in the majority of cases (Sosman).<sup>53</sup> Calcification of valves can be demonstrated by the regular fluoroscope with a 5-inch gap, 5 milliamperes of current, a small fluoroscopic aperture and a screen of fine grain and high intensity like the type B fluoroscopic screen. The most important step in the procedure is the proper accommodation of the observer's eyes by at least 15 minutes in a completely darkened room. The usual screen examination is then carried out, and the fluoroscopic aperture is narrowed to a few square centimeters. The intracardiac calcified deposits show a to-and-fro movement with systole and diastole; those in the valves may have an excursion of 2 or 3 cm., sometimes in an elliptic or triangular course. The calcified and aortic mitral valves are found under a line in the auriculoventricular sulcus, which is usually about 45° from the horizontal. The patient should be rotated slightly to the left, so that the calcified areas will not be hidden by the spine, and a deep inspiration should be taken and held so that the underlying pulmonary markings will be immobile and not confusing. A helpful means of differentiating between the calcified and mitral aortic valves is to rotate the patient to the opposite side (left anterior oblique), where the mitral valve will be found to be in the posterior third of the heart shadow, while the aortic valve will be in the middle third.

Calcification of the mitral annulus fibrosis, a frequent source of error, is usually U-shaped, J-shaped, or O-shaped, and is more homogeneous than the irregular mulberry-like calcification in the valves themselves; its movements are similar to those of the calcified mitral valve, but its clinical significance is relatively *null*, representing merely a senile change.

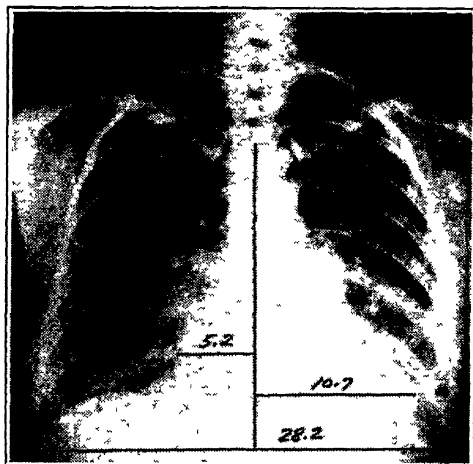


Fig 23—Case 3. Seven-foot film of heart showing slight cardiac enlargement, straight left border without convexities, and fairly marked dilatation of pulmonary vessels. Patient was symptomless at time. (Sosman: J. A. M. A.)

Dilatation of the left auricle does not result from calcification of this ring, as the function of the mitral valve is not affected. Calcification of sufficient amount to be visible fluoroscopically may also be found in (a) the coronary arteries, (b) the pericardium, (c) the myocardium, such as calcified infarcts, (d) the endocardium, particularly of the auricles, and (e) rarely in a benign tumor; but usually it is not confused with calcification in the valves. The finding of dilatation of the left auricle and calcification of the mitral valve renders the diagnosis of mitral stenosis unequivocal.

Conditions which may cause *dilatation of the left auricle*, and thus simulate mitral disease, are: Congenital heart dis-

ease, especially patency of the ductus arteriosus and pulmonic stenosis; scoliosis of the spine to the right, pleuropericardial adhesions, fibrosis of the left upper lobe, pneumoconiosis, emphysema, beriberi, and thyrotoxicosis. Patent ductus arteriosus may cause dilatation of the left auricle, as has been reported by Eppinger and Burwell.<sup>32</sup> In Sosman's experience, scoliosis, extrapericardial adhesions, pulmonary fibrosis, pneumoconiosis, and emphysema either fail to simulate the appearance of mitral disease or do so only but rarely; and thyrotoxicosis rarely causes changes in the cardiac contour which would simulate mitral disease except in failing hearts with auricular fibrillation. The most frequent cause of error in the diagnosis of mitral disease, however, is heart-failure from any cause, particularly with cardiac dilatation and auricular fibrillation; in such cases auricular dilatation may actually be due to relative mitral regurgitation or to stasis in the atonic fibrillating auricle. It has been shown, however, by Sussman and Woodruff<sup>54</sup> that fibrillation of the auricles is rarely followed by dilatation of the auricles unless complicated by valvular disease. Moderate degrees of left auricular dilatation may be present in ambulatory patients with heart-failure due to nonvalvular lesions, such as beriberi, anemia, or nephritis.

Since mitral stenosis is of slow, gradual development, it is quite possible that routine use of the fluoroscope by a trained observer may be of aid in *earlier diagnosis*. There is little of therapeutic value in earlier diagnosis; the chief value lies in the difference of *prognosis*, with a possible change in ideas as to the latent or inactive period in potential heart disease (the period between the first infection with rheumatic fever and the onset of symptoms or the discovery of physical signs of acquired valvular heart dis-

ease) In this latent stage the difficult differential diagnosis is between no heart disease with a normal prognosis and acquired mitral valvular disease with a bad prognosis as to length of life

### Rheumatic Heart Disease in Children

A follow-up study by Stroud and Twaddle<sup>55</sup> of children with rheumatic heart disease treated at the Children's Heart Hospital, Philadelphia, during the 15 years between 1922 and 1937, revealed 144 deaths, the greatest number of which resulted from congestive heart-failure (104 patients), 11 apparently died of acute rheumatic infection without signs of decompensation, 9 died of bacterial endocarditis (3 acute and 6 subacute), 9 died suddenly (1 from a pulmonary infarct, 5 from embolism, and 3 from causes not definitely stated), 5 died of pneumonia and 6 of noncardiac causes. The greatest mortality occurred between 3 to 5 years after the primary manifestation of rheumatic fever. The youngest patient to die was 5 years of age; and the oldest 28 years. Eighty-one per cent of deaths occurred before the age of 16, with the heaviest grouping between the ages of 8 and 16 years. Of those who died of congestive heart-failure, auricular fibrillation was present in 13; absent in 19, and there was no record for the remaining 72 cases. In 5 cases auricular fibrillation started shortly before death, 4 had had fibrillation for some time—1 for as long as 5 years. The ages of onset of auricular fibrillation were: 1 at 7 years, 1 at 8 years, 3 at 13 years, 1 at 16 years, 1 at 19 years, and 1 at 23 years. It appears that the children who live through the adolescent period have a good chance of reaching maturity. There was no apparent indication that the children in whom rheumatic fever occurred early in childhood

have a shorter span to live than those in whom the onset of the disease came later. If the patients are divided into 2 subgroups, 1 with onset ages of 3 to 7 years and the other with onset ages of 8 to 12, those in the latter subgroup have the highest percentage mortality during the first 6 years of the disease.

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## ENDOCRINOLOGY

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### THE ADRENALS

*By* MAX A. GOLDZIEHER, M.D.

**Physiology** — Recent investigations have added evidence to the view that the variegated functions of the *adrenal cortex* are not performed by a single hormone but by several separate, although probably chemically closely related, factors (Goldzieher<sup>1</sup>). Fractionation of cortical extracts by Mason and Kendall, Reichstein and others,<sup>2</sup> has yielded several sterols such as corticosterone, desoxycorticosterone and at least 4 other crystalline compounds of varying biological activity. The most active of these crystalline substances, however, assays only 3 to 4 rat units per milligram as compared to 20 to 30 rat units per milligram for

certain amorphous fractions or to the higher activity of the crude, unfractionated extract. This might be attributable to the presence of various esters of corticosterone, the activity of which is enhanced by esterification (Kuizenga and Cartland<sup>3, 4</sup>). The differences between various fractions of the cortical extract are not only quantitative but also qualitative in respect to different phases of activity, such as maintenance of electrolyte balance or body weight and production of adrenal or thymus atrophy (Wells and Kendall<sup>5</sup>).

It is believed that maintenance of *electrolyte (Na,K) balance in the body* and the *control of water metabolism* are

the pre-eminent tasks of the cortex. Investigations by Hartman and his associates<sup>6, 7</sup> have shown that extracts of the cortex yield 2 separate fractions: one which maintains life in the adrenalectomized animal in spite of low blood sodium levels and another which specifically acts upon and maintains the sodium concentration of the plasma at its normal level. The sodium factor is also capable of maintaining life in the adrenalectomized animal in the same way as it is achieved by mere administration of sodium salts but only if environmental conditions are not adverse, for the animals kept alive on the sodium factor do not appear to be quite normal. Moreover, relatively large amounts of the sodium factor must be given for maintenance, whereas much smaller amounts suffice in the presence of the other cortical factor. Thus, it seems that the sodium factor is more effective in the presence of the second, life-maintaining principle.

Similar differences are noted in respect to the effect of the various cortical products upon *carbohydrate metabolism*. Native cortical extracts are diabetogenic and so is corticosterone, whereas desoxycorticosterone appears to be ineffectual (Long, Katzin and Fry<sup>8</sup>). Glyconeogenesis is strongly stimulated by Hartman's<sup>9</sup> cortin fraction and but slightly by his sodium factor, which seems to correspond to desoxycorticosterone. It must be emphasized, however, that the effects of cortical hormone upon carbohydrate metabolism are simulated, at least partly, by sodium, probably indirectly through potassium effects which are operative in the chemical reactions concerned with the formation or utilization of glucose (Kendall<sup>10</sup>).

The *multiplicity of cortical hormones* is not universally accepted and it has been maintained "that the adrenal cortex as it normally exists in the adult, elab-

orates only 1 hormone which suffices to maintain all the normal functions of the organism" (Grollman). This statement, however, disregards the fact that the cortex produces substances which affect the gonads and the genital apparatus not only under pathologic conditions, but also in the course of ordinary physiologic events.

The *effects of cortical extracts on the reproductive system* vary to a considerable degree. Gonadotropic effects, such as increase in the size of epididymis, seminal vesicles, prostate and penis in male animals, as well as formation of lutein bodies and changes of the endometrium in females, have been observed. The luteinizing effect of both cortical extracts and synthetic cortical sterols has been shown by several investigators; this is in accord with the fact that cortical sterols and progesterone are closely related chemically. Their biological interrelationship is borne out by the observation that increased progesterone production in the pregnant animal or injection of progesterone is capable of relieving adrenal insufficiency in the adrenalectomized animal (Looney<sup>11</sup>).

The nature of the *sex factor* present in, or produced by, the normal adrenal gland is still obscure, although evidence points to "compound E" (Kendall<sup>10</sup>), one of the crystalline fractions of the cortical extract. Oxidation of this substance yields adrenosterone, a definitely androgenic substance which has been directly isolated from the cortical extract (Reichstein). Other androgenic substances (isoandrosterone, transdehydroandrosterone, etc.) were found in the urine of patients presenting the adrenogenital syndrome and disappeared upon removal of an adrenal cortical tumor. The direct isolation of estrone and progesterone from the adrenals (Beall<sup>12</sup>) leaves no

doubt that this gland is a source of sex hormones. It is believed that all these hormones are derived from a common mother substance, probably Kendall's compound E (Marker<sup>13</sup>).

The significance of the adrenal cortex for the *development and function of the reproductive system* is well borne out by pathological observations concerning the production of excessive and probably abnormal cortical hormones, accompanied by premature sexual development in the male child and masculinization of females, both young and adult. Feminizing effects, claimed to obtain in case of adrenal tumors in adult males, are still open to doubt.

Hormone assays in cases of *tumors or hyperplasia of the adrenals* associated with virilism reveal an excess of androgen in urine. The substance responsible for the androgenic effects was identified as a 17-ketosteroid (Callow<sup>14</sup>). Smaller amounts of such ketosteroids together with other androgens and estrogens are also found in castrates, as evidence of their common extragonadal origin. That this common source is the adrenal is quite probable, for the urinary excretion of steroids is considerably lower in Addison's disease. The secretion of androgen from the adrenals is amenable to suppression by hormonal control, for intensive estrogenic therapy seems to decrease the titer of androgens in the urine (Hamblen, Pattee and Cuyler<sup>15</sup>).

Much speculation has arisen concerning the relationship of the *adrenal sex sterols and the "cortical hormone."* Biologically active cortical extracts or their fractions (corticosterone, desoxycorticosterone) show no visible effects on the sexual organs. It is in accord with this fact that the production of the electrolyte-controlling and life-maintaining cortical hormone can be completely dissociated from the secretion of the sex sterol. This

was demonstrated but recently in cases of macrogenitosomia in which precocious puberty and genital enlargement were the results of a tumor of the adrenal cortex, yet in spite of the overabundance of pathological cortical tissue, control over electrolyte and water balance was lost. The patient displayed marked hunger for sodium salts together with symptoms of Addison's disease which eventually terminated fatally under the manifestations of adrenal insufficiency. Such cases seem to prove that the adrenal cortical tissue produces at least 2 different hormones, one of which might be discharged in excess while secretion of the other is fatally inadequate (Wilkins, Fleischmann and Howard<sup>16</sup>).

The urinary excretion of androgenic substances, especially 17-ketosteroids, has aroused considerable interest. The ordinary biological methods of assay on capons or other castrated animals are difficult and hardly practicable for clinical use. This explains the favorable reception of the newer colorimetric methods based on Zimmerman's reaction. These procedures seem to be accurate and offer greater possibilities for clinical studies for they also permit of distinguishing between the various androgenic fractions of the urine (Baumann and Metzger<sup>17</sup>).

### Pathological Physiology

**Adrenals in Acute Infections**—The significance of the adrenals in acute infectious conditions is beginning to receive more attention. Remarkable effects were obtained with *desoxycorticosterone* as well as with *cortical extracts* in patients with *lobar pneumonia, bronchopneumonia, gripe* and a number of severe infections. This treatment helped to maintain normal blood-pressure, appetite and a sense of well-being; it avoided circulatory collapse and toxicity;

it decreased the incidence of complications and shortened convalescence (Perla and Marmorston,<sup>18</sup> Hick and Barnes<sup>19</sup>). **Cortical extracts** seem to be particularly efficacious in combination with **vitamin C**, a combination which has become quite popular abroad, especially in the treatment of *diphtheria*, while its significance in chronic infections such as *tuberculosis* appears to be established (Pottenger).

**Adrenals in Nutritional and Infectious Disorders of Early Infancy**—The rôle of cortical function in the nutritional and infectious disorders of early infancy has also aroused interest. Treatment with **adrenal extracts**, **vitamin C**, **salt and glucose** seems to produce outstanding results (Szasz<sup>20</sup>). These findings support the view that the sudden postpartum involution of the adrenal cortex sets up a state of physiologic insufficiency, which accounts for the lability of water and salt metabolism, the tendency to dehydration and gastrointestinal symptoms, and the general vulnerability of the infant by adverse environmental influences. This vulnerability prevails until the physiologic involution of the cortex is terminated and the slow process of rebuilding the permanent adrenal cortex gets well on its way.

**Adrenals and Hypertension**—It is generally accepted that hypertension may arise as a complication of adrenal cortical hyperactivity, especially in the presence of a cortical tumor. The connection between hypertension and medullary hyperactivity, however, is still controversial, excepting cases of paraganglioma, associated with the symptom-complex of paroxysmal hypertension. Contrary to earlier skepticism, the pathogenetic significance of pheochrome tumors found either within or in the vicinity of the adrenals is admitted (Howard and Barker; Nuzum and Dalton<sup>21</sup>). The

paroxysmal attack of hypertension characteristic for these adrenalin-producing tumors is occasionally associated with a peculiar irregularity of the cardiac rhythm (Burgess, Waterman and Cutts).

The relationship of hypertension to overactivity of the *adrenal medulla* is tacitly implied by the increase in volume of surgery performed on the abdominal sympathetic for the purpose of reducing blood-pressure. A recent survey of 264 cases showed that **splanchnic sympathectomy** reduced blood-pressure in over 43 per cent of the cases with visible improvement of circulation as demonstrated by ophthalmological methods (Braden and Kahn<sup>22</sup>). The results were maintained for a period of at least 2 years.

The *renal* type of *hypertension*, experimentally produced by interference with renal circulation (Goldblatt), seems to be the result of the action of a pressor substance circulating in the blood. The degree of the response to this still hypothetical renal factor is largely determined by the reaction of the adrenal glands (Page<sup>23</sup>; Williams, Diaz, Burch and Harrison<sup>24</sup>).

### Diseases of Adrenals

**Addison's Disease — Diagnosis** — Cases of *forme fruste* of Addison's disease or non-addisonian hypoadrenia would be recognized more often if better diagnostic methods were used. Cutler, Power and Wilder's<sup>25</sup> test determines the diminished ability of the patient to conserve sodium chloride; the test is of definite diagnostic value and easier to perform than Zwemer's potassium tolerance test. The latter, however, is more likely to detect minor deviations of cortical function, especially if variations of the blood potassium level are checked by simultaneous determination of blood sodium values (Goldzieher<sup>26</sup>).

Abnormal potassium curves were obtained also in cases of *chronic bromism*, while an apparently normal potassium tolerance was noted in a few cases of Addison's disease (Greene, Levine and Johnston<sup>27</sup>). These findings, however, do not diminish the diagnostic significance of the potassium tolerance test. The low potassium values observed in hypercortical conditions (Power and Kepler<sup>28</sup>) are also in favor of the potassium tolerance test as a measure of cortical function, the value of which is not made doubtful by the fact that low potassium values were also noted in cases of Addison's disease energetically treated with cortical extracts (Hoffman<sup>29</sup>).

**Treatment**—The modern treatment of chronic adrenal insufficiency of the classical addisonian type is based generally on the understanding of cortical function; it utilizes a *diet* low in potassium, high in sodium, and relies upon the effects of *cortical extracts* or *synthetic desoxycorticosterone* (Thorn and Fitor<sup>30</sup>). The effectiveness of this treatment is recognized, yet many investigators are far from enthusiastic and do not accept administration of either desoxycorticosterone or the highly purified cortical extracts as complete replacement therapy (McCullagh and Ryan,<sup>31</sup> Thompson and associates<sup>32</sup>). The use of desoxycorticosterone offers the advantage of greater potency with smaller volume of the injection material. On the other hand, there is the disadvantage of the danger of massive edema and increase of the blood-pressure to abnormally high levels, occasionally complicated with cardiac failure (Ferrebee and associates<sup>33</sup>).

Another shortcoming of desoxycorticosterone is its ineffectiveness upon the disturbances of carbohydrate metabolism; this may be one of the reasons why the synthetic compound, in contrast to the

cortical extracts, does not improve general well-being, gastric functions and nutritional state of the patient (Gordon<sup>34</sup>).

Implantation of pellets of desoxycorticosterone is just as effective as continued injection of the substance (Thorn<sup>35</sup>). It is claimed that the rate of resorption from the pellets is slow enough to prevent untoward by-effects. It would seem, however, that the criticism which applies to the treatment with injections also confronts the implantation therapy, for desoxycorticosterone is not the equivalent of adrenal cortical secretion. Optimal results might be obtained by combining implantation with injections of cortical extracts or even better, with oral administration of cortical preparations.

**Hypoadrenia** — Hypoadrenia of a lesser degree which does not correspond to the *forme fruste* of Addison's disease is being recognized more and more as the cause of varied clinical manifestations. Hypoadrenia may be the expression of a constitutional weakness or the result of acquired exhaustion of the cortex in the course of excessive physical or nervous strain or as the aftermath of some debilitating disease.

The response of such patients to treatment with *cortical extracts*, either by the parenteral or oral routes, is truly gratifying. Startling improvement was obtained in chronically fatigued, neurotic patients by oral therapy alone (Huddleson and McFarland<sup>36</sup>) and similar results were reported on the treatment of *asthenia* (Gordon, Sevringhaus and Stark<sup>37</sup>) and *status lymphaticus* (Campbell<sup>38</sup>). A deficiency of vitamin storage seems to run parallel and warrants the addition of *cevitamic acid* (Gordon, Sevringhaus and Stark<sup>37</sup>).

The significance of hypoadrenia in the early forms of *toxemia of pregnancy* has

received additional clinical support. The therapeutic results reported by Kotz and Kaufman<sup>39</sup> in 50 cases of *hyperemesis of pregnancy* treated with *interrenin*, orally or parenterally, sound fully convincing.

**Adrenogenital Syndrome**—The original concept of the adrenogenital syndrome included only precocious puberty and virilism, both attendant to adrenal cortical tumors; the syndrome is now generally extended to comprise also pseudohermaphroditism and virilism due to cortical hyperplasia, diabetes of the bearded woman (Achard-Thiers), and Cushing's syndrome (Broster<sup>40</sup>). The significance of excessive or abnormal activity of the adrenal cortex in such cases is illustrated by the high concentration of 17-ketosteroids in the urine, demonstrable by colorimetric methods (Crooke and Callow<sup>41</sup>).

**Diagnosis**—The adrenogenital syndrome in *childhood* is recognized by virtue of symptoms of precocious puberty. *Pubertas praecox* is the proper designation for the disease in male children, but does not do justice to the symptoms prevalent in female children who, as a rule, show no breast development nor enlargement of the uterus or menstrual bleeding. The term, *pseudoprecocity*, suggested by Reilly, Lissner and Hinman<sup>42</sup> emphasizes the essential difference between the manifestations of the disease in the 2 sexes. The powerful development of the musculature characteristic of the male "infant Hercules" is not equally consistent in female patients. This is readily explained in those cases in which the cortical lesion is malignant and precipitates cachexia instead of muscular overdevelopment. In the presence of benign tumors or a sufficiently prolonged course of the disease, female patients also develop a masculine figure

and considerable muscular strength (Lukens and Palmer<sup>43</sup>).

**Adrenal Cortical Tumors—Treatment**—The results obtained in the *surgical treatment* of adrenal cortical tumors are showing considerable improvement. The earlier primary mortality has disappeared, since the patients are given, preoperatively, sodium salts, a low potassium diet and cortical extracts, in other words, the standard treatment for adrenal insufficiency (Walters and Kepler<sup>44</sup>). The need for this *preoperative treatment* is explained by the fact that these tumors produce an excessive amount of hormone which depresses the pituitary and shuts off the supply of corticotrope hormone to the adrenals. Hence, the atrophy of the adrenals and their inability to resume function upon surgical removal of the hormone-producing tumor.

**Adrenal Virilism** — Refeminization with loss of body hair and resumption of menstrual function has been noted in adrenal virilism following varied surgical procedures on the adrenal glands. In addition to the *removal of tumors, unilateral adrenalectomy* or *bilateral resection of hyperplastic adrenals* was also performed; a summary of 40 cases was published recently by Reilly and his associates. The association of *virilism with hypertension and diabetes* (Achard-Thiers) has also received more attention (Shepardson and Shapiro<sup>45</sup>); consequently, even milder cases of this condition are being recognized with greater frequency.

### Adrenal Gland Therapy

**Dosage**—Adequate dosage of cortical hormone in the treatment of *Addison's disease* is the prerequisite of success. Hard and fast rules are difficult to establish in view of the varying potency

of the commercially available extracts and the equally variable responsiveness of the patients. By far larger dosage is required in the state of crisis or at times of exacerbation of symptoms such as occurs in the course of infections, adverse climatic influences, physical exertion, or as the result of dietary indiscretions.

The opinions about substitution of desoxycorticosterone acetate for the extracts are at variance. According to Thorn, 1 mg. of the synthetic product is the equivalent of 3 cc. of Wilsons' cortical extract, Thompson found the relation to be more nearly 1 to 1. The majority of Thorn's patients did not require more than 5 to 6 mg. of the crystalline substance; they needed from 10 to 25 mg. daily during a crisis or period of increased stress. The appearance of edema makes it necessary to cut the daily dose to 1 or 2 mg.; simultaneously, sodium salts should be used sparingly, not to exceed 5 Gm. daily in addition to that already contained in the food, while the potassium intake should not be reduced below 4 Gm. daily.

If desoxycorticosterone is used in *pellet form*, the need for daily injections is obviated. Pellets of 150 mg. content and of standard size are inserted subcutaneously in the infrascapular region. The rate of absorption is calculated to be from 0.25 to 0.35 a day and assumed to be constant. By increasing or decreasing

the number of pellets, the maintenance dose is supplied; it seems to be considerably less than in the injection treatment.

Desoxycorticosterone caused marked chloride retention in a few cases, yet did not influence the symptoms, whereas addition of cortical extract brought about marked clinical improvement without a distinct shift in chloride balance (McCullagh and Ryan<sup>81</sup>). Such observations suggest that combination of desoxycorticosterone acetate in less than the maintenance dose with injection and oral administration of cortical extracts is the optimal therapeutic procedure. Constant control of blood-pressure and sodium chloride balance yields information to show whether the dosage is excessive, or inadequate; it will also afford a guide in determining the need for additional sodium salts or restriction in potassium intake.

The milder forms of *hypoadrenia* call for commensurately smaller amounts of cortical hormone; the need for the synthetic product will arise but seldom. Two to 5 cc. of a potent extract given 2 to 3 times weekly is enough in most cases, especially if cortical extracts are also given orally. The latter suffice for maintenance as soon as the initial injections have brought about improvement, but injections must be resumed if the oral medication fails to maintain progress.

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## CHORIONIC GONADOTROPIN

By WILLARD O. THOMPSON, A.B., M.D.

The gonadotropic material prepared from the urine of pregnant women is the most potent of all the gonadotropic products that have been made available commercially. Because of its origin from the chorionic villi in the placenta, it is called *chorionic gonadotropin* and it is

available under a variety of trade names, *i. e.*, korotrin, follutein, A. P. L., pranturon, antuitrin-S, etc. Extensive observations have been made by the reviewer with the first 4 products and all of them have been found to be potent. An international standard has been pre-

pared, 1 unit of which represents the gonadotropic activity of 0.1 mg of the Standard Preparation established by the Permanent Commission on Biological Standardization of the Health Organization of the League of Nations.

**Physiological Action** — Chorionic gonadotropin stimulates primarily the interstitial cells in the testis and promotes luteinization in the ovary. It thereby differs from the gonadotropic materials of menopausal and castrate urine, which produce a follicle-stimulating effect in the ovary and a stimulation of spermatogenesis in the testis, while the material from the pituitary itself and that from the serum of the pregnant mare produce both follicle-stimulating and luteinizing effects. In actual practice it has not been possible to produce much stimulation of gonadal function with gonadotropic material from the pituitary and from the serum of the pregnant mare. Chorionic gonadotropin, however, produces very effective stimulation.

**Indications**—In the male it is used in the treatment of *secondary hypogonadism* requiring stimulation therapy, notably in *cryptorchidism*, in hypogonadism secondary to hypopituitarism and in certain selected cases of *impotence in later life*. In the female its uses are not clearly defined, although improvement has been reported in some cases of *menorrhagia* associated with incomplete luteinization.

**Undescended Testes**—Most reports on the treatment of cryptorchidism appear to be overenthusiastic. Descent is reported in 60 per cent of cases on the average, whereas the writer has been able to produce descent in only 20 per cent of all of his cases and in only 27 per cent of those under 16 years of age. The inclusion of many cases of pseudo-cryptorchidism may account for some of the high percentages of successful results

reported. Accurate diagnosis is very important in evaluating treatment. Migratory testes are not true undescended testes and at the time of puberty move permanently into the scrotum without treatment. After only a few injections of chorionic gonadotropin they will also remain in the scrotum, perhaps only to become migratory again when treatment is discontinued. True cryptorchidism is not present unless it is impossible to displace the testis into the scrotum in any position of the body.

Treatment with chorionic gonadotropin appears to cause descent only of those testes which would descend spontaneously at the time of puberty without treatment, *i. e.*, of those testes not retained by mechanical factors. However, the treatment does have the following advantages:

1. In about one-fourth of the patients it causes the testis to move into its normal environment without any other form of therapy.

2. It makes it possible to determine at an early age what patients will require surgical correction and thus bring the testis into its normal environment as early as possible.

3. By enlarging the parts involved, it facilitates operative procedures even when it does not produce descent of the testis.

The treatment should be started at the earliest age at which operative procedures are feasible, *viz.*, at about the age of 3 years. The effective dose varies from 100 to 1000 I.U. daily, depending upon the susceptibility of the testes to stimulation. When descent occurs from glandular therapy it usually does so within 2 months, although much longer periods of treatment are necessary in some patients. The genitalia must be carefully watched and treatment stopped before excessive genital growth is pro-



duced. The growth stops as soon as the stimulus is removed. It is usually necessary, however, to produce a moderate amount of growth in order to cause descent of the testis. Since operative procedures are necessary in about three-fourths of the cases, the treatment involves the intelligent combination of glandular therapy and surgery. Glandular therapy should be continued up to the time of operation. If any delay ensues, regression in the size of the genitalia may increase the technical difficulties of the operation.

Little is known about the effect of premature stimulation with this material on the function of the testis in later life. So far as personal observations go, they indicate that if the treatment is carefully controlled, it is beneficial and not harmful. The writer has not observed any serious emotional or social complications of the sexual stimulation resulting from its use.

**Fröhlich Syndrome**—There is much discussion at present as to just what the diagnostic criteria are for the diagnosis

of the Fröhlich syndrome in the absence of a pituitary tumor. Many obese boys undergo changes in body contour at the time of puberty. However, there is no doubt that in some obese boys with narrow shoulders, full breasts, large abdomen with a transverse fold just above the pubic area, broad hips, large thighs, small genitalia and genu valgus, the daily administration of from 1000 to 2500 I.U. of *chorionic gonadotropin* will produce some development of the musculature of the body, decrease in size of the breasts, development of the genitalia, some increase in height and narrowing of the hips, straightening of the legs, and growth of hair all over the body. To be most effective, the treatment should be begun at about the time the changes of puberty normally begin, *i. e.*, at about the age of 10 or 11 years. It is usually desirable to supplement this form of therapy with the administration of a suitable weight-reducing *diet*. When the *basal metabolism is low*, it is also desirable to administer enough *desiccated thyroid* to raise the rate to normal.

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## EQUINE GONADOTROPIN

### (Gonadotropic Hormone of Pregnant Mares' Serum)

By GEORGE JOYCE HALL, M.D.

In 1930, Cole and Hart reported, in the first of a series of papers, that the blood of the pregnant mare, between the fortieth and one hundred and fiftieth days of gestation, contained a hormone which they thought was similar to that found in human pregnancy urine. Further papers in their series, as well as reports by numerous other investigators, notably Evans, confirmed the presence of a gonadotropic hormone.

The equine gonadotropic hormone was shown to have a characteristic biological reaction similar to that of the an-

terior pituitary gonadotropic complex itself. Administration of proper dosage to female rodents produced follicle growth, ovulation and corpora lutea in the manner and sequence found in adult females.

The primary difference between the equine gonadotropic hormone and the chorionic hormone from pregnancy urine becomes evident in their effects upon hypophysectomized animals: chorionic gonadotropic hormone has little, if any, effect on the gonads, while the equine hormone restores complete normal func-

tions in ovaries atrophied by hypophysectomy.

These various animal experiments indicated that this gonadotropic hormone might be valuable for clinical use. Purification of the hormone, to a degree that it would be unlikely to produce foreign protein reactions, made its clinical use in the human possible.

This serum is considered to be of value in *ovarian hypofunction*. Functional disturbances of menstruation and female sterility due to reduction of pituitary-ovarian function, therefore, would be the indications for its use clinically. It has been successfully used in some cases of *amenorrhea*, *hypomenorrhea*, *oligomenorrhea*, *menometrorrhagia* and *dysmenorrhea*—and in *hypovarian sterility*.

A number of investigators have reported obtaining varying results with the gonadotropic hormone of pregnant mares' serum. Among those who have published some favorable results are Hall<sup>46</sup> and Novak,<sup>47</sup> Shorr,<sup>48</sup> Hamblen.<sup>49, 50</sup>

Among others who have reported both good results and failures are Greenblatt and Torpin,<sup>51</sup> Huber and Davis,<sup>52</sup> and Sevringhaus.<sup>53</sup>

Most investigators have reported in literature only a few cases or a relatively small series, the writer's report,<sup>46</sup> of 135 cases being the largest.

Careful examinations must be made in every practical way before any hormone therapy is planned for any patient, and this is more important regarding gonadotropic therapy. Before treatment of any patient with a gonadotropic hormone, all physical possibilities as causes of her trouble (or partial causes) must either be ruled out or corrected. Each patient must be routinely examined regarding endocrine functions and for pathological conditions. Certainly there

is no point in treating *sterility* with gonadotropins if both tubes are occluded.

Although basal metabolic rate determinations only occasionally show great variations, all patients should be tested for their rate of oxygen metabolism. Examination of patients who complain of sterility should include routinely, besides the basal metabolism rate, an investigation of the cervix, cervical canal, general bimanual examination and tubal patency test. Some investigators, in the determination of tubal patency, prefer a hysterosalpingogram instead of a Rubin test, because a better idea of the uterine cavity is obtained. Endometrial biopsies are done routinely by many, but others do not consider the endometrial pattern to be sufficiently diagnostic, although a record of endometrial biopsies is of help in some cases as an aid in evaluating the effect of therapy. There is a lag in some patients in the time of endometrial response following therapy, and this must be considered in determining the effect of treatment.

Sperm counts must be made of the husband's ejaculatory fluid, and the quality of the spermatozoa determined before active therapy is administered to the wife.

Hamblen,<sup>54</sup> in the discussion of endocrine therapy of functional ovarian failure, reported that whereas occasionally sexual maturation followed equine gonadotropic therapy in young women with classical hypovarianism, the majority of these women failed to obtain any signs of ovarian stimulation. He further stated that (1) normal ovaries do not require therapy, whereas ovaries which have failed do not necessarily preserve the receptivity of normal ovaries; (2) no proof has been submitted that even when receptivity of ovaries to equine gonadotropins exists, ovulation and proliferation of corpus luteum may

be induced, except occasionally as a part of response of certain patients with classical hypovarianism; *i. e.*, equine gonadotropins, even under most favorable circumstances, may not do a full job of complementing pituitary deficits. Six months previously<sup>50</sup> he had reported that "equine gonadotropins have a definite place in the rational endocrine therapy of sterility" (presumably when due to hypogonadotropic activity of the pituitary), "but constitute only one of the endocrine methods of therapy. When doubt exists as to the responsiveness of ovaries to gonadotropic influences, a therapeutic trial of equine gonadotropin is indicated."

Following the administration of the hormone to rats (21 to 23 days old) in daily doses for 60, 90 and 123 days which yielded ovaries weighing about the same as those of control rats, Flumann<sup>55</sup> was disappointed, having apparently overlooked the cyclic requirements for ovarian maturation and ovulation. He now administers the hormone to his patients over a period of only 3 to 5 days for each course of treatment.

The author has used the hormone in over 400 cases and has yet to experience unpleasant serum reactions except in 2 patients who had developed urticaria at previous times, and both of these developed mild generalized urticaria after 3 doses of the hormone.

Erving and his associates<sup>56</sup> feel that the reports by those investigators who expressed enthusiasm or optimism do not offer conclusive evidence of the value of equine gonadotropic hormone in stimulating ovulation in women; and they then report a series of 48 cases of sterility, dysfunctional flowing, and amenorrhea, in which 81.2 per cent were apparently unaffected. They apparently relied entirely on endometrial biopsies as functional tests, reporting "secretory

endometrium," "proliferative" endometrium and "hypoplasia," but apparently the endometrial pattern made no difference in their plan of therapy. They then concluded that the hormone has not been shown to stimulate ovulation in women with anovulatory bleeding or amenorrhea, nor that it had any apparent effect in cases of sterility.

The writer's report<sup>46</sup> of 135 patients treated with the serum showed:

Menstrual disturbances 31% improved, 58% cured.

Genital hypoplasia 17% improved, 47% cured.  
Sterility 55.8% cured.

Since this report was presented (May, 1939), 173 other patients have been treated with essentially the same results excepting a higher percentage of pregnancies in sterility and a reduction of 25 to 30 per cent of dysmenorrhea cures. It is possible that the preparation used here being 2000 I.U. per cubic centimeter, the dose being greater than that used by other investigators, may account for a belief that there are fewer "nonreceptive" or "nonresponsive" ovaries than is the general opinion.

Gray,<sup>57</sup> whose report seems to depend entirely on *endometrial biopsies* as clinical tests before and during the period of therapy, is not satisfied with his results. It is unfortunate that the endometrial biopsy is used so trustingly as an accurate clinical test when so many have agreed with Kotz and Parker,<sup>58</sup> who concluded that there are no specific endometrial patterns for gynecological symptoms.

The vaginal epithelium is much more dependable, and the vaginal smear technics of Papanicalou and of Shorr.<sup>59</sup>

And the simple 2 per cent aqueous fuchsin staining technic used in the writer's laboratory gives reliable, quick information (Shorr).

"Besides anterior pituitary gonadotropic extracts, concentrates from the serum of pregnant mares will accomplish stimulation of testes or ovaries in the human" is the conclusion of Sevringhaus.<sup>53</sup>

The writer disagrees with those authors who limit the use of this hormone to cases of *amenorrhea*, *menorrhagia* and *sterility*. Dysmenorrhea is one of the most difficult conditions to cure, but there is a group of patients that responds well to substitution therapy either with the *estrogens* or with *progesterone* or both. These patients are not cured, however, until the substitution therapy has been administered long enough to result in 3 or 4 comfortable menstrual cycles, followed by the equine gonadotropic material as indicated. Adequate therapy for several months has brought on cures in about 50 per cent of the cases. This is particularly true of those patients who have genital hypoplasia. These patients need large doses of estrogenic substance during the postmenstrual phase for a sufficient period of time to develop normal-sized uteri, before gonadotropic hormones may be expected to accomplish the desired result. In order to be considered cures there must be satisfactorily stimulated ovarian and uterine functions, permitting the continuance of normal ovarian and menstrual functions without further therapy.

Empirically arranging vaginal smears into 7 types, from the most pronounced atrophic type as found in late cases of artificial menopause as type 1 plus (1 +) up to the best possible type of epithelial cornification as the normal or 7 plus (7 +), permits an accurate estimate of the degree of efficiency of the therapy that has been administered.

**Administration** — Substitution therapy is administered in all functional hypövarian conditions until such time as a

5 +, 6 +, or 7 + vaginal smear has been obtained, before any anterior pituitary gonadotropic factor or equine gonadotropic hormone is indicated. The exception to this is in *menometrorrhagia*, in which *prolactin* is used (see elsewhere in this volume), until all bleeding ceases, and then the gonadotropic hormone is given during the proper portions of the subsequent ovarian cycles. Some authors persist in publishing directions for daily administration of this hormone for 10 to 20 days each menstrual month. This is entirely unphysiological. It is necessary to use the material only between the fifth and eleventh days from onset of menstruation. If small doses of from 200 to 300 I.U. are used, it may well be given daily from the fifth or sixth to the tenth or eleventh days; if 500 I.U. are given at each dose it can well be done on the seventh, eighth, ninth and tenth days; and if 2000 I.U. are administered at each dose, it may be done on approximately the eighth, ninth and tenth days from the onset of menstruation. There is no logic that would allow its administration long enough to prevent maturation of the follicle or ovulation or corpus luteum formation.

After having used over 12,000 doses of this hormone and completed the treatment of slightly more than 400 patients (Dec. 1, 1940) the results (when doses of 2000 I.U. each are used) are as follows: There have been cures of 25 per cent in *primary amenorrhea*; 66.7 per cent in *secondary amenorrhea*, 60 per cent in *hypomenorrhea*, 60 per cent in *oligomenorrhea*, 90 per cent in *functional menometrorrhagia* (following the use of prolactin), 50 per cent in *dysmenorrhea*, 60 per cent in *genital hypoplasia*, and 70 per cent in *sterility*. There has been a noticeable improvement in the percentages of improved and cured patients with

the higher potency doses of 2000 I.U. than previously, although it seems to require just as many months of therapy.

To all patients showing less than normal estrogen blood level (as evidenced by vaginal smears) estradiol benzoate in the form of *progynon B* is administered routinely until good vaginal cornification occurs. Except in amenorrhea, 10,000 R.U. of progynon B are given about 48 hours after menstruation has ceased and repeated every fourth or fifth days, for, as a rule, not more than 3 doses per cycle. Because this occasionally causes early menstruation, it then becomes necessary to change by giving only 2 doses of 10,000 R.U. 5 days apart, followed by 2 doses of 2000 R.U. at the same interval, with about 10 mg. of *progesterone* (poluton) with the last dose of estrogen. This is frequently varied by giving the progesterone orally as *pregneninolone* 5 mg. daily with *progynon DH* tablets 0.5 mg. daily—during the premenstrual 5 or 6 days. This plan permits more assurance of obtaining secretory endometrium, than by using only the 3 large doses of estrogen. If on the fifth to the seventh day after the last muscular injection the vaginal smear is a normal progestational type,

then the gonadotropic material is administered after the next period of menstruation. Vaginal smears are taken on the fifth to the seventh day after the last of each monthly series of injections of serum. If all subjective symptoms have disappeared, and when the vaginal smear is normal for that portion of the cycle, treatment is stopped. Vaginal biopsy is a more accurate guide than an endometrial biopsy, but vaginal biopsies and vaginal smears correspond quite accurately. Serum therapy is not continued longer than 4 months; if a cure has not been effected, the patient is asked to return for further therapy after a wait of 4 to 6 months.

After allowing a rest period for several months for some of the patients whose ovarian disturbances were not corrected, Krohn has repeated the routine series of treatments and has effected some cures. He has had "very good results in those cases of menorrhagia and amenorrhea due to a hyperhormonal state frequently associated with polycystic ovaries, also, a moderate number of successes with sterility problems of the anovulatory type, where all other causes had been eliminated by careful routine investigation.

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## CLINICAL USE OF EQUINE GONADOTROPIC HORMONE IN THE MALE

By L. F. HAWKINSON, M.D.

Thus far few reports have appeared on the use of gonadotropic hormone from pregnant mares' serum in the male.

Kundstadter<sup>60</sup> reported that in a group of 12 boys between the ages of 6.5 and 14.75 years with hypogenitalism, 8 showed improvement. In 7 cases of true cryptorchidism, complete descent occurred in 3 and partial descent in 2 patients.

The reviewer has had limited success with equine gonadotropic hormone in boys. Only 2 of 8 patients have shown definite improvement after 8 to 10 months of treatment. Until more is known as to the effect of this hormone on the immature testis, it should be used with caution in the young male. Results in a small series of cases would indicate that prolonged treatment is necessary.

The use of the equine hormone in the correction of faulty *spermatogenesis* has often been striking. A definite increase in the number of sperm, improvement in motility, and decrease in the number of abnormal forms have been obtained in the majority of cases treated. The dose has been 400 to 500 I.U., intramuscularly, 2 to 3 times a week. If no improvement in the semen picture was apparent in 6 to 8 weeks, further treatment was usually of no avail. The continued use of large doses after the sperm count has been increased to normal may result in a marked drop in the count.

Looney<sup>61</sup> has described a case in which the sperm count was increased

from 36 million per cubic centimeter to more than 133 million per cubic centimeter with marked improvement in motility. The abnormal forms decreased from 48 per cent to less than 20 per cent.

Three of 5 of Charny's<sup>62</sup> patients treated with equine gonadotropic hormone showed an improved semen count, and all patients presented histological evidence of stimulation of the seminiferous tubules. The latter was determined by testicular biopsy and is a significant finding.

The status of the equine gonadotropic hormone in other conditions in the male has not been determined.

## MALE SEX HORMONE

By CHARLES W. DUNN, Ph.G., M.D.

### Sterility in the Male

Kreutzmann<sup>63</sup> divided sterility in the male in 2 chief groups, urologic and endocrinologic. Occasionally malnutrition or vitamin deficiency may cause sterility but it occurs so infrequently that for practical purposes it need not be stressed. If urologic examination is negative, it may correctly be assumed that some endocrine dysfunction is present. This supposition can be proved by an examination of the sperm. In a study of the ejaculate the 3 most important factors are the number of sperm per cubic centimeter, the percentage of abnormal forms, and the degree of motility. The previous concept of a man being sterile if the sperm count is below 60,000,000 per cubic centimeter has been shown incorrect by Hotchkiss's<sup>64</sup> study of 200 men. Fertility is impaired when abnormalities reach from 20 to 22 per cent and clinical sterility is usually present if more than 25 per cent abnormal forms are found. All patients showing abnor-

malities of the ejaculate can be classified into 4 groups:

1. Normal sperm count and normal percentage of abnormal forms with a lowered B.M.R.
2. Oligospermia and a normal percentage of healthy sperm.
3. Normal number of sperm with an increase of abnormal forms.
4. Oligospermia with an increase of abnormal forms.

Fifteen per cent of the patients were in group 1, having a basal metabolism rate varying from minus 10 to minus 18. They were all given thyroid by mouth, following which the desired results were obtained. It is in groups 2, 3 and 4 that occasional brilliant results, but mostly failure, are reported after the administration of endocrine products. The administration of endocrine products at the present time is entirely experimental. Patients receiving the same androgen or gonadogen for the same condition react differently. In some instances there will be an increase in the number of sperm,

whereas in others there will be no change. Marked increase in the number of abnormal forms may also occur in one man while a decrease will result in another.

The clinician must guard against the inclination to use large doses of androgens, estrogens and gonadotrophic agents or to administer them continuously for long periods. Kreutzmann has seen aspermia develop in a patient with 34 per cent abnormal forms after receiving 0.5 cc. of chorionic gonadotrophin 3 times weekly for 2 months. Examination of the same patient a year later showed only a few sperm present with 25 per cent abnormal forms. Another patient with 26 per cent abnormal forms received 2 cc. of pregnant mares' serum 3 times a week for 1 month. Following the injections the abnormal forms increased to 74 per cent. After a rest period of 1 month they dropped to 31 per cent. Testosterone propionate was injected 3 times weekly in 5 mg. doses for 1 month with no consistent change in the abnormal sperm of 6 patients after the administration of the drug. In 2 patients with an increased number of abnormal sperm before treatment the drug caused a further increase in pathologic cells, while in the third patient there was no change. In view of the harm that may occur, the indiscriminate injection of endocrine products should be stopped. It is advisable to make repeated sperm analyses during the administration of these potent drugs in order to guard against transient or possible permanent damage to the spermatogenic structures of the individual.

**Value of Testicular Biopsy in Male Sterility**—Charny<sup>62</sup> states that testicular biopsy gives the most direct evidence of the actual state of spermatogenesis. It is especially valuable in male

infertility under the following circumstances:

- 1 In azoospermia, to differentiate between the obstructive and nonobstructive types.
- 2 In oligozoospermia, to differentiate between faults in spermatogenesis and post-inflammatory obstructive lesions of the ejaculatory ducts
- 3 To observe the severity of the pathologic process and thus determine the capacity of the tubules to regenerate.
- 4 To evaluate by repeated biopsies the efficacy of the various extracts recommended for stimulation of spermatogenesis.

No regeneration can be expected in the seminiferous tubules that have undergone complete atrophy, no matter how effective the therapeutic agent may be. Increased cellular activity in the seminiferous tubules affected by therapy and demonstrated by testicular biopsy is true evidence of the effectiveness of the agent employed.

Five patients presenting varying degrees of faulty spermatogenesis, as judged by semen examination and testicular biopsy, were given 400 I.U. of *gonadotropic hormone of pregnant mares' serum* intramuscularly 3 times a week for 3 weeks. Subsequent injections were administered intravenously thrice weekly for approximately 2 additional months, at which time a second testicular biopsy was done. Only 3 of the 5 patients showed an improved semen picture following the mare serum hormone therapy, but all presented histological evidence of stimulation of the seminiferous tubules. These results are sufficient evidence to suggest that the administration of hormone of pregnant mares' serum deserves further trial as a spermatokinetic agent.

### Testosterone Propionate

**Indications — Male Climacteric** — Thomas and Hill<sup>65</sup> treated 2 cases of involutional melancholia with testosterone

TABLE I  
OBSERVATION OF SPERMATOKINETIC EFFECT OF GONADOTROPHIC HORMONE OF PREGNANT  
MARES' SERUM IN 5 INFERTILE MALES

Patient	Before Treatment		After Treatment		Changes in Tubular Activity as Observed by Testicular Biopsy
	Semen Volume in cc.	Sperm Count per cc.	Semen Volume in cc.	Sperm Count per cc.	
1. G. C.	2.5	16,400,000	3.5	29,600,000	Increased
2. D. M.	1.0	1,100,000	2.0	2,900,000	Increased
3. O. D.	2.5	4,600,000	2.5	4,300,000	Increased
4. J. B.	3.5	500,000	5.0	6,400,000	Increased
5. D. K.	3.5	10,100,000	3.0	29,000,000	Increased

propionate. One male, age 56, suffered from nervousness, insomnia, occipito-cervical headache and lapse of memory, as well as delusions of persecution. He was first given 10 mg. testosterone propionate 3 times weekly for 4 weeks, then 10 mg. twice a week for 6 weeks, at which time he was discharged as normal and he has remained in good health and of stable mind. Another male, age 48, suffered a loss of memory during the past 6 months, increasing emotional instability, insomnia and delusions of persecution. He was given 10 mg. of testosterone propionate weekly for 8 weeks. After discharge, improvement continued.

**Premenopausal Dysfunctional Uterine Bleeding**—Mazer and Mazer<sup>66</sup> feel that, although the cause of uterine bleeding in instances of small intramural fibroids may be dysfunctional and often amenable to endocrine therapy, a *preliminary curettage* is nevertheless imperative. The occurrence of metrorrhagia in a premenopausal woman after repeated episodes of delayed menstruation may be considered dysfunctional in type if the presence of pregnancy is first eliminated.

While *testosterone propionate* (total of 50 to 200 mg.) does not invariably relieve dysfunctional uterine bleeding at any dosage level, it does so in 50 per

cent of the patients who submit to a month's treatment. In the female, doses of 450 to 1000 mg. over a period of a month produce atrophy of the endometrium, temporary amenorrhea through inhibition of the pituitary-ovarian mechanism and, in many instances, facial hair growth, enlargement of the clitoris, a husky voice and a decrease in the size of the breasts. Smaller doses (50 to 200 mg. in a month) produce no discernible effects other than the control of dysfunctional metrorrhagia. The endometrial pattern and menstrual rhythm are undisturbed and masculinizing manifestations do not appear. Its influence is temporary and lasts only long enough to permit natural readjustment and cannot rejuvenate aging ovaries of premenopausal women nor stimulate the ovaries of younger women to biphasic activity.

A cure was considered to have been effected if the abnormal uterine bleeding ceased during the month of treatment and did not recur for at least 3 months after its withdrawal. Forty-two of 64 patients (66 per cent) were cured and 22 (34 per cent) were not cured or were only temporarily improved. Twenty-seven of the 35 women who were curetted prior to testosterone therapy remained well during the follow-up period of 3 or more months after with-



drawal of treatment, whereas only 15 of the 29 noncuretted group remained well. In 25 per cent curettage alone arrested the dysfunctional uterine bleeding for a period of 3 or more months, at least sufficiently long for the endocrine imbalance to adjust itself.

Larger doses of testosterone (total 300 to 600 mg.) did not yield better results than the smaller doses. About 10 per cent of the menopausal patients who receive large doses of estrogen for severe climacteric symptoms bleed profusely and almost incessantly during and even after withdrawal of treatment because of the pronounced endometrial hyperplasia. In many of these patients the

addition of 10 mg. of testosterone propionate to each dose of estrogen for a period of a month effectively arrests the bleeding and prevents its recurrence.

No constitutional ill-effects were observed in any of the 64 patients. In only 2 was there a temporary delay in menstruation (total doses in excess of 300 mg.). No obvious tendency toward reduction of fertility in those who received smaller doses was observed. There was no tendency to abortion. The tendency to virilism was noted in 2 of the 20 patients who had received total doses in excess of 300 mg. There was a definite decrease in the pitch of the voice of 2 others.

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## FEMALE SEX HORMONE

By CHARLES W. DUNN, Ph.G., M.D.

**Physiological Action of Estrogen—Effect on Uterus and Anterior Pituitary**—Zondek<sup>67</sup> believes that conclusions concerning humans cannot be drawn from results in mice and monkeys. He has given large doses of estrogens to humans and has never encountered any changes of the uterus which resulted from the alleged carcinogenic action of estrogens. In 2 cases he found that the administration of 1,200,000 I.U. of estradiol benzoate produced an inhibition of the development of the uterine mucosa in women and increased the number of mucous glands of the cervix but did not induce any changes of a carcinomatous nature. In another case he tried to inhibit the growth of carcinoma by very large doses of estrogens. He found that the normal ovarian cycle in women can be inhibited by estrogen (at least 70,000 I.U.) and artificial amenorrhea can be produced by postponing menstruation for from 7 to 70

days. The estrogen administered blocks the gonadotropic secretion of the anterior pituitary which prevents the development of the corpus luteum and progesterone production. Still larger doses of estrogen (more than 600,000 I.U.) are able to cause the uterine mucosa to react with glandular cystic hyperplasia owing to the local effect of the hormone. Doses of 6,000,000 I.U. over 60 days induce functional castration or hormonal sterilization by preventing the ripening of the corpus luteum formation. The cervical glands react to estrogen with marked enlargement. The administration of 1,400,000 I.U. of estradiol benzoate during the course of 28 days does not bring about any changes in the portio. The administration of 6,000,000 I.U. during 60 days induced the formation of a large, partly papillary, erosion of the portio, which demonstrated that an erosion of the portio can be caused by hormonal irritation. Even extremely

large doses of estrogen did not cause carcinomatous changes of the uterus.

**Indications — Functional Menometrorrhagia**—Ryan<sup>68</sup> obtained gratifying results from the use of cyclic **estradiol benzoate** and **progesterone therapy** in 10 cases of functional menometrorrhagia. The cyclic use of sex sterols in the treatment of functional menometrorrhagia developed as a consequence of finding low urinary assays for estrogenic substances in such a case, which was confirmed by assays in other cases and has been correlated with endometrial biopsies. The following therapy has been effective when large doses of A. P. L. have failed:

Treatment may be initiated at any time, even during an episode of metrorrhagia, since estrogen injections are usually sufficient to stop hemorrhage. Injections are then given on the basis of a 28-day cycle, 2000 R.U. of estradiol benzoate given 2 or 3 times weekly during the first 3 weeks. During the fourth week 2 to 5 I.U. of progesterone are given on the fifth and third days before the onset of the calculated menstrual period. Therapy is then withheld for 3 or 4 days, after which the course is again initiated without regard for the presence or absence of bleeding and is repeated on the above-mentioned 28-day basis. When a fairly definite cycle is present or has been established, it has been Ryan's custom to give the estrogen and progesterone only during the 2 weeks preceding menstruation in total divided dosage of 4000 to 8000 R.U. of estradiol benzoate and 2 to 10 I.U. of progesterone. With this method estradiol benzoate and progesterone should probably be given concurrently during the fourth week on the fifth and third days premenstrually. After 4 to 6 months of such cyclic usage, therapy

should be withheld for a time to determine whether or not a normal rhythm and flow have been re-established.

Ryan states that it is preferable to do a **curettage** before beginning therapy with hormones, especially in women over 30 years of age, where malignancy has to be considered more seriously than in younger women.

**Dysmenorrhea** — Sturgis and Albright<sup>69</sup> believe that relief of dysmenorrhea from estrin therapy is associated with a consistent change in ovarian function. The presence of an apparently normal corpus luteum seemed to be a prerequisite for the occurrence of cramps. Estrin therapy was apparently followed by a cramp-free period only when it prevented the development of a functioning corpus luteum during that cycle. Dysmenorrhea could be induced in a patient having anovulatory periods by the administration of a sufficient amount of progesterone. Twenty-five cases with disabling dysmenorrhea were administered 10,000 R.U. **progynon B**, injected intramuscularly every third day. A series of injections consisted of from 3 to 14. If the first of a series of 6 to 10 or 12 injections was given within the first week after the onset of menses, the next period was invariably free from uterine cramps. If the series was not started until 2 weeks after the onset of the previous flow, there was no change in the pains during the subsequent bleeding. The dependence of this result on the timing of the injections during the cycle suggested that the effect might be related to the action of estrin upon ovulation. Endometrial biopsy taken before a painful period showed evidence of ovulation, whereas every biopsy obtained after treatment and before a cramp-free period showed no evidence of ovulation. When biopsies were taken in 3 consecu-

tive months, the estrin treatment 1 month did not inhibit or repress the occurrence of ovulation the next month. The sixth day seemed to be the latest which would give dependable results.

In a few patients who had repeatedly responded to treatment in the past, the optimum number of estrin injections was followed by daily injections of 5 mg *progesterone (proluton)* for 5 days. Although they had been entirely free from cramps previously after the estrin

alone, the progesterone caused a return of the cramps in 2 of 3 cases.

The evidence from endometrial biopsies has led to the conclusion that ovulation is a *sine qua non* of all types of essential dysmenorrhea. The inhibition to the pituitary must take place before the ovarian follicle has received an adequate growth stimulus by FSH. The same mechanism appears to explain why it was possible to suppress ovulation 2 months in succession.

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## HYPERPARATHYROIDISM

By HENRY L. JAFFE, M.D.

**Differential Diagnosis**—It is to be assumed that before treatment is begun, the question of differential diagnosis has been carefully considered and the case definitely established as one of hyperparathyroidism. It is immediately helpful to remember that this disease is, after all, relatively uncommon. Because of this fact, in weighing whether a given obscure case is or is not one of hyperparathyroidism, the burden of proof lies upon the affirmative side.

In this connection, it should be borne in mind that while the presence of a *hypercalcemia* is strong evidence in favor of a diagnosis of hyperparathyroidism, hypercalcemia is not infrequently found also in cases of multiple myeloma and, though rarely, in cases of carcinoma extensively metastatic to the skeleton. If these other possible causes of hypercalcemia are kept in mind, the likelihood of confusing with hyperparathyroidism cases of *multiple myeloma* or *skeletal carcinosis* will be greatly diminished. *Paget's disease per se* should likewise no longer be confused with Recklinghausen's disease of bone (hyperparathyroidism with pronounced skeletal manifestations). In uncompli-

cated cases of Paget's disease the serum calcium values are normal. Very rarely, however, a case of Paget's disease is encountered in which routine biochemical study reveals a definite hypercalcemia. These cases must be interpreted as instances of Paget's disease complicated by hyperparathyroidism or at least instances of the coexistence of the 2 diseases in the same subject.

A condition which is frequently and unnecessarily misdiagnosed as hyperparathyroidism is *polyostotic fibrous dysplasia*, which the writer's associate, L. Lichtenstein,<sup>70</sup> named and described in detail, emphasizing especially its pathology. Clinical reference to the condition had previously been made under such names as "*unilateral fibrous osteodystrophy*," "*unilateral Recklinghausen's disease*," "*disseminated osteitis fibrosa*," "*osteitis fibrosa in multiple foci*," etc. The condition is a skeletal developmental anomaly affecting several or many bones, with predominantly unilateral involvement.

The affected bones show filling of their medullary cavities by gritty grayish-white fibrous tissue containing trabeculae of newly formed primitive bone.

Islands of cartilage may also be found in the fibrous tissue filling the marrow cavity. The condition apparently results from perverted activity of the specific bone-forming mesenchyme. It usually manifests itself in childhood or early adult life and evolves slowly, pursuing a protracted clinical course characterized by pain, deformity, and a tendency to pathologic fracture of affected bones. Precocious menstruation in girls suffering from severe forms of the disease has been described by Goldhamer, by Borak and Doll, and more recently by Albright and his associates. The presence of hyperpigmentation of certain areas of the skin, apparently due to excessive melanin content, has also been mentioned by Goldhamer and particularly stressed by Albright and his colleagues. The precocious menstruation and hyperpigmentation apparently are seen only in very severe cases whose clinical manifestations have begun very early in life. It is probable that the precocious menstruation and other endocrine phenomena, manifested in only a small proportion of these cases, result from involvement of underlying skull bones. Such cases represent instances of particularly severe polyostotic fibrous dysplasia with secondary phenomena due to damage of the base of the brain and possibly to nerves. It should be borne in mind that the great majority of cases of this disease show no such secondary phenomena, and that, indeed, even the osseous changes may be limited to a few bones developing from a single limb bud.

It is because roentgenographically the affected bones appear widened, show thinned cortices, and often present appearances suggesting the presence of cysts that these cases are so often misinterpreted as instances of hyperparathyroidism. At least 6 cases of the 22 which have come under the writer's ob-

servation had previously been thus misdiagnosed and consequently had been subjected to a vain search for a parathyroid tumor. The fact that the lesions are unilateral or mainly unilateral and that the unaffected bones are normal should be enough to exclude hyperparathyroidism. Furthermore, the serum calcium value is normal in practically all cases of polyostotic fibrous dysplasia. Occasionally, however, it may be slightly above the upper limit of the normal. For instance, it was 11.0 mg. in 1 case observed.

**Types — Primary vs. Secondary Hyperparathyroidism** — Recent advances have shown more and more clearly that cases of hyperparathyroidism fall into 2 categories, *i. e.*, primary (or idiopathic) and secondary. The *primary* (or idiopathic) cases are those in which the point of departure for the disease is apparently the parathyroid glands themselves, since there is no known explanation of what instigates their hyperfunctioning. The parathyroid abnormality in cases of primary hyperparathyroidism may be of the nature of (1) a tumorous growth (an adenoma) usually limited to a single gland, but sometimes affecting 2 glands, or (2) a hyperplasia affecting all (*i. e.*, the theoretical 4) parathyroids. The secondary cases are those in which the point of departure for the disease is elsewhere than in the parathyroid glands themselves. Actually, it seems to be exclusively in connection with renal insufficiency of longstanding that a pronounced secondary hyperplasia may be observed of all (the theoretical 4) parathyroids, resulting in a complicating or secondary clinical hyperparathyroidism.

The division into primary and secondary parathyroidism thus is made on the basis of absence or presence, respectively, of some plausible instigating factor for the parathyroid hyperfunctioning.

Anderson<sup>71</sup> has reviewed the whole question of hyperparathyroidism in relation to renal disease. Castleman and Mallory point out further that there are certain differences in histologic detail, in the parathyroids, between the primary and the secondary cases of hyperparathyroidism when the parathyroids show diffuse hyperplasia. In the primary cases the hyperplastic glands are composed of water-clear cells, while in the secondary cases they are composed of small chief cells.

As a clinico-pathologic complex, however, hyperparathyroidism in its full efflorescence has 3 central facets, *i. e.*, parathyroid, renal, and skeletal alterations. This is true whether the case being dealt with is a primary or secondary hyperparathyroidism. Thus, in a case starting out as an instance of primary hyperparathyroidism the kidneys may become so severely damaged that the consequent renal insufficiency in turn increases the parathyroid hyperfunctioning and thus exacerbates the whole state of hyperparathyroidism. On the other hand, in a case starting out as an instance of hyperparathyroidism secondary to renal disease, the parathyroid hyperfunctioning that may develop may become so pronounced that it, in turn, also acts powerfully upon the bones.

Thus, altogether, there are some fully evolved cases in which it cannot be said, from the total clinical complex presented or from the biochemical findings as to the blood, whether the hyperparathyroidism which is being dealt with is primary or secondary. This fact has important bearings upon the questions of therapeutics and prognosis. In cases of primary hyperparathyroidism, if the offending parathyroid tissue is removed, improvement of the renal function can be expected unless the kidneys have been damaged irrevocably. On the other

hand, in cases of hyperparathyroidism secondary to renal insufficiency of longstanding, removal of enlarged parathyroids is attended with considerable risk and little promise of benefit unless the basic renal disease can first be successfully treated.

**Treatment—1. Parathyroidectomy**—Specifically in relation to treatment, let it be assumed first that a case under discussion is one of primary hyperparathyroidism. In at least 4 out of 5 such cases, the offending parathyroid tissue consists of a single *parathyroid adenoma*. Often, this adenoma is easily located, but occasionally it is aberrantly situated, notably in the superior mediastinum. To forestall disappointment in case the adenoma cannot be found at the first operation and to leave the prospect open for a second operation involving the mediastinal approach, it is advisable to suggest from the beginning, to the patient or to the responsible relative, that a two-stage operation may be necessary. When the adenoma is removed, the pathologic state is abruptly arrested and soon begins to be reversed.

If, as is sometimes the case, the primary hyperparathyroidism is being caused by *idiopathic parathyroid hyperplasia* instead of adenoma formation, the surgical treatment presents particularly knotty problems. This is so because all 4 of the glands may be hyperplastic and there is danger of intractable tetany if all 4 are removed. On the other hand, if all 4 are not enlarged, there is no assurance that the remaining gland or glands will not subsequently undergo hyperplasia and thus induce recurrence of the symptoms. Personal experience with a case of this type (seen through the courtesy of Drs. Ottenberg and Garlock), in which only 2 hyperplastic glands were removed at first, was that there was a rapid recurrence of all the

manifestations of the hyperparathyroidism within a few months. In this case, at a subsequent operation the surgeon removed a third enlarged parathyroid gland and all but a tiny fragment of the fourth. Several bits from the removed part of the fourth were then immediately transplanted into pockets made in the sternocleidomastoid muscle, and the mouths of these pockets were closed with black silk ligatures to mark their position. In this site (or in pockets in the abdominal wall) the transplants would be easily accessible should their removal be indicated later on. In the case in question, such removal had not proved to be necessary up to 1 year after the original operation. In any event, in these cases, the surgeon must recognize the danger on the one hand of recurrence of the hyperparathyroidism from regrowth of the remaining stump, and on the other of the development of intractable hypoparathyroidism from damage to the essential remaining tissue. In the case just mentioned, the operation was followed by a period of hypocalcemia and tetany which, though difficult to control at first, became easier to manage after about 3 months. From then on, under therapy, the calcium level has remained high enough to avoid tetany, or even carpopedal spasm, though the Chvostek sign could be elicited from time to time. Now, about 1½ years since operation, the serum calcium, inorganic phosphate, and phosphatase values have finally become normal.

Let it now be assumed that the case is one of secondary hyperparathyroidism following upon chronic renal insufficiency. In such a case, attention should be concentrated upon improvement of

the renal function, if that is possible. As to the parathyroids, it is questionable whether they should be touched at all in any case of renal hyperparathyroidism (renal dwarfism of childhood or its equivalent in adults). Any improvement effectable in the renal function, however, will be strongly reflected in diminution of the parathyroid hyperfunction.

**2. Management of Postoperative Complications**—Attention has already been called to methods for combatting *postoperative hypoparathyroid tetany* with *soluble calcium salts* given by mouth or intravenously, with or without supplementary *parathyroid extract*, subject to control by determination of the serum calcium value. A more recent but already well-established addition to the armamentarium against the tetany is **A.T. 10 (*dihydrotachysterol*)**. The optional dose varies widely, depending upon the severity of symptoms and the degree of hypocalcemia. Its indiscriminate use, either alone or in combination with other drugs intended to combat the hypocalcemia, is fraught with the danger of hypercalcemic intoxication. In using dihydrotachysterol it should also be borne in mind that its effect is cumulative, so that its use must be controlled by periodic determinations of the serum calcium value. An initial dose of 5 to 10 cc. daily by mouth for 3 or 4 days, to be followed by a maintenance dose of 2 cc. twice or thrice weekly for a time, can be expected to control the tetany in most cases. There is no evidence of harmful effect of this maintenance dose, even if used over a long period, provided that the dosage is properly controlled by serum calcium determinations

## THYROID GLAND

By CHARLES WILLIAM DUNN, Ph.G., M.D.

### Thyroid Gland and Unexplained Fever

In patients who have a moderate rise in temperature ( $99^{\circ}$ - $100^{\circ}$  F.— $37.3^{\circ}$ - $37.8^{\circ}$  C.) for which there is no explanation, Moehlig<sup>72</sup> found an enlarged thyroid gland, usually adenomatous in character; an increase in the pulse rate, around 80 to 100 per minute; and a fine tremor of the extended fingers. The basal metabolism rate; blood count, particularly the leukocyte and differential count; x-ray findings of the chest; blood sugar; blood Kahn test; nitrogen, urine and undulant fever tests are all normal. The fever frequently follows an infection, such as tonsilitis, influenza or pyelitis, and is usually considered by the physician as one which he cannot locate. *Thyroidectomy* in these patients results in the temperature becoming normal within a week and remaining so thereafter.

### Cretinism

**Treatment**—Shelton<sup>73</sup> reports the case of a 10½-year-old female child with all the physical and mental stigmas of cretinism. Anterior *pituitary extract*, ½ dram (2 cc.), said to contain 10 growth units per cubic centimeter, was injected subcutaneously daily. There was no carpal advancement though there was some increase in size. No improvement in general physical and mental status occurred and the growth increment was in the range of normal expectancy. The following year 1 grain (0.06 Gm.) U.S.P. *thyroid* was administered daily. At the end of a year the x-rays showed marked enlargement of the 2 original carpal centers with 3 new well-developed centers and ossification of the distal epiphysis of the ulna. There

was some mental development and a gain of 6 inches in height and 8 lbs. (3.6 kg.) in weight. The following year 2 grains (0.013 Gm.) *thyroid* were administered daily and resulted in the development of 2 new carpal centers in the wrist, with much greater massing of the entire carpal structure, a height gain of 4 inches, a weight gain of 8 lb. (3.6 kg.) and some mental improvement. The following year *vitamin B complex* was added as well as a preparation containing 1000 I.U. of B<sub>1</sub> per day. At the end of the year there was additional massing, with beginning ossification of the pisiform, a height gain of 3.3 inches (8.5 cm.), a weight gain of 12 lb. (5.4 kg.), with an improvement in the general appearance and mental improvement. In 3 years there was a growth of 13.3 inches and an advance of 9 years in the bone age.

### Thyroid Gland Therapy

#### Indications—*Pituitary Dwarfism*

—The case of a girl, age 13 years, who was markedly retarded physically, has been reported by Looney.<sup>74</sup> Her sexual development was that of a girl of 10 years. At 6 years of age she was given *pituitary* powders by mouth. The blood chemistry determinations gave high values for cholesterol, chloride and phosphorus and a low level for calcium. The basal metabolism rate was normal. She was given ½ grain (0.03 Gm.) *thyroid* every other day and *cod-liver oil*, 1 tablespoonful t. i. d. and *brewer's yeast*, 1 tablet, t. i. d. Intramuscular injections of *polyansyn* containing 40 U. of growth factor were given every other day. Rest periods of 30 days were given. After 4 months an increase in height of ¾ inch (2 cm.) was noted and a gain

of 6½ lb. (3 kg.) in weight. She was taken off polyansyn and placed on *growth hormone*, 50 U. every other day. This was increased to 100 U. and in 6 months to 200 U. or ½ dram (2 cc.) of growth factor 3 times weekly. The thyroid was increased to 1 grain (0.06 Gm.) every other day and then to 1 grain (0.06 Gm.) daily. The Brewer's yeast tablets were increased to 6 tablets daily and she was given 30 grains (2 Gm.) *dicalcium phosphate* daily. Since treatment began the patient has gained 3¾ inches (10 cm.) in height and 26 lb. (11.8 kg.) in weight, but she still shows a deficiency of 1¾ inches (4.3 cm.) in height and 6⅓ lb. (2.9 kg.) in weight for the minimum for her age. The author believes that growth in this case was a direct response to the medication.

Twenty children showing signs of pituitary dwarfism, ranging in age from 11 to 17 years, were treated by Lurie<sup>75</sup> over a period of from 7 to 40 months with *growth complex*, in average dose 1 cc. twice a week, with the addition of *thyroid extract* and *extract of whole pituitary* orally. No more than 3 grains (0.2 Gm.) of desiccated thyroid extract or 6 grains (0.4 Gm.) of whole pituitary extract were given daily. All but 2 of the children gained 42.6 per cent more than the expected normal increment of growth for like ages and periods of time. No appreciable gain in height was made during the periods when oral therapy alone was administered. The failure of 2 patients to gain more than the normal increment can be attributed to the fact that the epiphyses were already practically closed in 1 case and in the second case to lack of co-operation on the part of the patient. It should be remembered that failure to grow normally may be due to a variety of causes, external as well as internal. Failure to obtain results

from therapy is very often due to failure to understand the nature of the factors responsible for the deficiency in growth.

**Thyroid Medication During Childhood**—*Thyroid deficiency* causes a retardation of growth, dentition, osseous and mental development and the condition is sometimes unsuspected until the child is 3 or 4 years old. In the first and second years adequate thyroid treatment offers the most favorable prognosis. Unless there is a definite retardation in the osseous development, growth, dentition and mental development, cretinism can be excluded. Changes of the skin and hair and apathy are common to hypothyroidism. A serum cholesterol above 300 mg. per 100 cc. is strongly suggestive of hypothyroidism. Adequate dosage with thyroid causes striking clinical changes, a marked acceleration of growth and osseous development and a drop in the serum cholesterol. If hypothyroidism exists and thyroid is discontinued, the patient becomes more sluggish, weight will increase rapidly, the color of the skin and lips will fade and, finally, the skin will become cool, rough and dry. Most characteristic of all, after the withdrawal of thyroid, the serum cholesterol will rise to high levels.

In *juvenile hypothyroidism* the patient seems to have grown and developed during the first few years of life. Later there is a slowing or stopping of growth and development and the child lags further and further behind the normal for his age. The child looks much younger than his actual years, is stunted in height, with skeletal proportions corresponding to his height rather than to his age, is of stocky body build, overweight but not obese, mentally retarded, has a dull expression, and there is a marked delay in osseous development, second dentition, etc. These changes are usually much less marked than in cretinism,



according to Wilkins.<sup>76</sup> Deviation from the characteristic clinical picture may occur. Of still greater diagnostic importance is the additional finding in some cases of a porous, stippled or fragmented appearance of the osseous centers. Serum cholesterol is subject to wide spontaneous fluctuation so that at times it is within the normal limits. The urinary excretion of creatine is greatly diminished or absent. The most important criterion for diagnosis is a specific response to comparatively small doses of thyroid.

*Desiccated thyroid* by mouth is the therapeutic agent of preference. A single daily dose is as efficacious as divided doses. The rate of growth development is largely governed by thyroid activity. If less thyroid is given than is required to maintain a normal level of metabolism, the developmental rate will be slower than normal. The small doses cause disappearance of the cretinoid facies, the changes of the skin, hair and other obvious signs of cretinism, but do not cause the child to grow and develop at a normal or slightly accelerated rate, and they lead to the loss of much valuable time in the early years of life. As the tolerance increases, it is important to raise the dose in order to maintain an adequate rate of development. It is rarely, if ever, necessary to exceed 3 grains (0.2 Gm.) daily. The tolerance must be found by trial for each patient. The therapeutic dose should be maintained slightly below this level. The rates of growth and development should be constantly followed as a guide to the efficacy of therapy. With the beginning of effective treatment, considerable loss of weight and sweating may occur. Even with very small doses of thyroid, all obvious signs of hypothyroidism may disappear within a few weeks or months.

Roentgenograms should be taken to study the centers of ossification, first at intervals of 3 or 4 months, later every 6 months or year. The height should be recorded regularly and mental standardizations made from time to time. Unless there is a continuous rapid development of the osseous system, an attempt should be made to increase the dose of thyroid to a higher level, as the patient's tolerance may have increased. If the bone age exceeds the normal or advances too far beyond the height age, the dose should be decreased.

In cases of *cretinism*, the *prognosis* for attaining approximately normal growth and physical development is good, provided treatment is adequate and not too long delayed. Unfortunately, the prognosis is much poorer for normal mental attainment. As a rule, the earlier intensive treatment is begun, the better is the prognosis. However, it is probable that in some instances the thyroid insufficiency has caused an irreparable damage to the nervous system in the earliest months of infancy.

In *juvenile hypothyroid dwarfism*, adequate treatment usually brings about a spectacular and gratifying acceleration of growth. This continues until the osseous development reaches the stage of epiphyseal union, usually simultaneously with sexual maturation. The ultimate height that the patient attains depends on the amount of stunting before treatment, the age at which thyroid treatment is begun, and interrelationships with other endocrine glands. The prognosis for normal mental attainment is much better than in cretinism.

Wilkins states that osseous retardation alone does not prove thyroid deficiency, yet "the slowing of growth and osseous development may be the earliest evidence of hypothyroidism to become

manifest." The difficulty of making the *diagnosis* of mild thyroid insufficiency is stressed as well as the fact that it is sometimes necessary to administer thyroid empirically to determine the effect of therapy.

## BREAST PATHOLOGY IN RELATION TO ENDOCRINE DISORDERS

By CHARLES F. GESCHICKTER, M.D.

**Etiology**—Experimental evidence has confirmed the importance of the endocrines in the pathology of the mammary gland. Hartman and Speert<sup>77</sup> report that cyclic changes occur in the mammary gland of the monkey in relation to the estrogenic and luteal hormones. Dunn has produced another case of *gynecomastia* in a man receiving large doses of the synthetic estrogen, stilbestrol. The occasional occurrence of gynecomastia with tumors of the adrenal has been emphasized by Lisser, and Geschickter and Byrnes have described in detail the various changes in *chronic cystic mastitis* which may be produced in the rat by a combination of estrogenic and luteal hormones with estrogen stimulation overbalancing the luteal influence. That the changes of mammary dysplasia are due to endocrine overstimulation, which may subside with the menopause, has been indicated by Lindgren. This author found in women at autopsy that the incidence of cystic disease of the breast, whether occurring alone or in the association with carcinoma, was at its height at the climacteric, falling abruptly after the age of 50 years. For carcinoma, on the other hand, the frequency curve is high between 60 and 70 years. Morbidity curves among living women show a similar discrepancy and strengthen the hypothesis that cystic disease is of endocrine origin and liable to senile involution. Further evidence in regards to the endocrine basis of chronic cystic mastitis has been supplied by Bucher and

Geschickter.<sup>78</sup> These authors have reported urinary assays for estrogen and pregnanediol (an excretion product of progesterone and an index of corpus luteum function) on 27 patients. These assays indicate that the various forms of mammary dysplasia are due to a relative excess of estrogen, the estrogen values being normal or high and the pregnanediol values below normal.

**Treatment** — Endocrine therapy for benign conditions of the breast is receiving added emphasis. Hoffman<sup>79</sup> reports that injections of *testosterone propionate* and *testosterone acetate* in 28 cases of *hypertrophy of the male breast* were followed by complete regression in 12 cases and a reduction of more than 75 per cent in 9 others. In no case was there any gross evidence of testicular damage or arrest of the growth changes of puberty. The amount injected was 25 mg. of testosterone propionate or acetate twice weekly for 10 to 40 injections.

Various endocrine substances have been used in the therapy of *chronic cystic mastitis*. *Testosterone* has been recommended by Desmarest and Capitain<sup>80</sup> and by Loesser.<sup>81</sup> Recently, Atkins<sup>82</sup> has reported results in 34 patients treated with testosterone propionate, the doses varying from 400 mg. in 4 weeks to as high as 1200 mg. in 6 weeks. Twenty-five patients were benefited as far as the breasts were concerned but in 8 cases there was hairiness, amenorrhea and deepening of the voice which lasted

for as long as 9 months after the treatment.

Atkins<sup>82</sup> controlled his studies with breast biopsies before and after the treatment. One of his cases developed mammary cancer 10 months after treatment. This was 1 among 212 cases of *chronic cystic mastitis* followed for 3 years. Atkins has also reported recently on estrogen therapy. Fourteen patients were treated with 80 mg. of *estradiol benzoate* by injections in 4 weeks or by 280 mg. of *stilbesterol* by mouth in 8 weeks. Only 3 were improved and 4 became worse, while 7 remained the same. Geschickter and Lewis recommend only 12 mg. of *estrone* by injections over a period of 8 weeks. Atkins<sup>82</sup> total dose is nearly 100 times as great when the relative strength of estrone and estradiol are considered. If the beneficial action of estrogen therapy is through luteinization of the ovaries, it readily can be seen that the higher dose is contraindicated. Geschickter<sup>83</sup> has recently advocated *progesterone* as a more logical treatment in chronic cystic mastitis. In the last 2 weeks, in 1 or 2 successive cycles, 40 to 60 mg. are injected. The treatment has been used in 28 cases with good results.

### Cancer of Mammary Gland

**Etiology**—The rôle of the estrogens in mammary cancer has been intensively studied in the past 2 years. The occurrence of estrogenic mammary cancer in mice and rats, normally resistant to the disease, has been amply confirmed (Bonser, Cramer and Horning<sup>84</sup> in mice, and Geschickter in rats). Cramer has sought to show that the susceptibility in different strains of animals is dependent upon the influence of estrogen on the endocrine system as a whole, the organs most prominently affected being the pituitary body and the adrenal glands.

In the *adrenals* it was found that a degenerative change is induced by estrogens in the zona reticularis of the *cortex*, whereas the degeneration developing in mice with spontaneously developing cancer is in the medulla. Cramer<sup>85</sup> believes that the action of the adrenal cortex is to augment that of estrogen and that the changes in the zona reticularis accompanying estrogen are the results of overstimulation. The rôle of the *medulla* is to protect and the spontaneous atrophy of this part of the adrenal predisposes to mammary cancer in susceptible mice. Cramer and Horning<sup>84</sup> report that in adrenalectomized mice the response to estrogen is impaired and carcinogenesis delayed or prevented. In the *pituitary gland* under estrogen stimulation the acidophil cells are greatly diminished in number and may be so few that the enlarged glandular mass consists almost entirely to chromophobe cells. This is interpreted as an exhaustion through overstimulation of the acidophil cells. By administering an anterior pituitary factor, the so-called thyrotropic hormone, the spontaneous development of mammary cancer in a susceptible strain of mice could be prevented. Their essential conclusions are that the susceptibility to mammary cancer (1) is not a fixed and unalterable quality residing within the organism, but can be modified; (2) does not reside entirely—if at all—within the mamma; (3) is conditioned partly by a disturbance of the endocrine balance.

The importance of the *pituitary gland* in estrogenic mammary cancer has been emphasized by Lacassagne.<sup>86</sup> He cites the works of numerous investigators to show that if hypophysectomy is previously performed estrogens are without effect on the mammary gland. With certain estrogens, however, mammary carcinoma develops without marked pituitary changes. Asdell and Seiden-

stein found that injections of thyrotropic hormone, at a rate of 12.5 guinea-pig units weekly in young animals of a strain subject to cancer, did not counterbalance the effect on the mammary gland of a weekly injection of 50 gamma of estrone benzoate. While admitting the importance of the pituitary gland in the production of estrogenic mammary cancer, Lacassagne,<sup>86</sup> therefore, does not believe the thyrotropic hormone offers a method of curing or preventing the disease. He had similar disappointing results with the use of progesterone. On the other hand, Lacassagne and Raynaud<sup>87</sup> found that biweekly injections of 2 mg. of *testosterone propionate* from birth onward protected the susceptible animals from the development of spontaneous mammary carcinoma. The theory is advanced that the action of testosterone on the pituitary prevents the action of estrogen on this organ. Nathanson and Anderson<sup>88</sup> believe that they have succeeded by injections of male hormone in preventing the occurrence of mammary carcinoma in mice which have been pregnant once.

**Treatment**—Geschickter has tried *testosterone* therapy in patients with mammary carcinoma, giving injections of 25 mg. biweekly for periods of several months. Pellets of the hormone have also been implanted. Temporary benefits, usually lasting for 1 year, were observed in about one-fifth of the cases. Salzstein and also Adair have had similar experiences. *Roentgen castration* before the menopause in women with mammary cancer has been about as beneficial (Taylor).<sup>89</sup> Prophylactic castration at the time of mastectomy has been of no benefit despite the fact that Herrell has found that in women who have cancer of the breast only 1.5 per cent have had castration previously, whereas, in the

control group 15.4 per cent had been previously castrated.

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# GASTROENTEROLOGY

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## AMEBIASIS

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Amebiasis is the clinical term applied to the disease entity produced by the invasion of the tissues of man by the pathogenic ameba *Entamoeba histolytica* (Craig). The term includes all of the manifestations of the disease in contradistinction to the term "amebic dysentery," which merely represents 1 stage. The use of the 2 terms synonymously has been criticized, since this perhaps has tended to produce the concept that dysentery is the single manifestation of the disease. Craig has shown that whereas dysenteric manifestations of amebiasis are uncommon in temperate regions, a host of other milder gastrointestinal symptoms are the result of infection with the *Entamoeba histolytica*. This modern clinical conception of amebiasis, together with the determination by surveys of the widespread distribution of the *Entamoeba histolytica* throughout the temperate zones, has led to an increasing interest in the disease.

**Etiology**—There are 5 amebae that parasitize the intestinal tract of man, *i. e.*, *Entamoeba histolytica*, *Entamoeba coli*, *Endolimax nana*, *Iodamoeba butschlii*, and *Dientamoeba fragilis*. Of these, only the *Entamoeba histolytica* is pathogenic. The other organisms are considered to be harmless commensals. Craig considers that it is impossible for the *Entamoeba histolytica* to live in the intestinal tract for any considerable time without producing lesions in the intestinal tract even though no symptoms occur. In addition to this pathological evidence, the demonstration of cytolyzing substances from *Entamoeba histolytica*, as well as

the production of complement fixing antibodies, is further evidence of its pathogenicity. The well-known fact that diarrheal stools are likely to contain parasites of all kinds has led, in some instances, to a consideration of the pathogenicity of other species of the ameba, in spite of failure to produce disease in man and experimental animals with them. Rothman and Epstein<sup>1</sup> review the evidence for such consideration and present clinical evidence to support the thesis that amebae other than *Entamoeba histolytica* may at times be pathogenic. Such evidence is inconclusive at the present time, and until definite evidence is obtained of tissue invasion or the liberation of toxic materials by these other organisms, they must be regarded as harmless commensals. The main significance of these parasites in feces of patients is that their presence indicates the patient has ingested food or drink contaminated with feces and may likewise harbor *Entamoeba histolytica*. The chief problem involved with these parasites is their differentiation from the pathogenic *Entamoeba histolytica*.

The major differential characteristics of these intestinal ameba are presented in Table I.

**Geographical Distribution and Incidence**—That the parasites are probably world-wide in their distribution is indicated by the fact that the parasites have been found wherever surveys have been attempted. From the tropical zones where the highest incidence of the parasites is found, the numbers diminish as the outer zones of the temperate zones

TABLE I  
(Craig and Faust<sup>2</sup>: "Clinical Parasitology," Lea and Febiger, Phila.)

	Entamoeba Histolytica	Entamoeba Coli	Endolimax Nana	Iodamoeba Butschlii	Dientamoeba Fragilis
"Vegetative" or Trophozoite Stage—Unstained					
Size in microns	15 to 60 $\mu$	15 to 50 $\mu$	6 to 15 $\mu$	8 to 20 $\mu$	5 to 12 $\mu$
Motility	Active. Progressive and directional.	Sluggish. Rarely progressive and directional.	Sluggishly progressive.	Sluggishly progressive.	Active and progressive.
Pseudopodia	Finger shape. Hyaline and glass-like. Rapidly extruded.	Shorter and more blunt. More granular. Slowly extruded.	Blunt and hyaline. Very rapidly extruded.	Blunt and hyaline. Slowly extruded.	Blunt and leaf-like. Hyaline.
Inclusions	Red blood-corpuscles. No bacteria in fresh specimens.	Bacteria and other material. No blood-corpuscles.	Bacteria. No blood-corpuscles.	Bacteria. No blood-corpuscles.	Bacteria. No blood-corpuscles.
Nucleus	Invisible usually	Visible	Visible	Invisible	Invisible
"Vegetative" or Trophozoite Stage—Iron Hematoxylin Stain					
Nuclear membrane	Delicate. Inner surface has single layer of minute chromatin dots.	Thicker; inner surface lined with coarse chromatin dots.	Intermediate in thickness. Chromatin seldom present on inner surface.	Thick. Chromatin dots may be present on inner surface.	Very delicate. No chromatin dots on inner surface.
Karyosome	Minute and in center of nucleus.	Much larger and eccentrically situated.	Larger and may be in center or to one side of center of nucleus.	Large and granular, in center of nucleus or somewhat eccentrically placed.	Larger and composed of definite chromatin granules lying in a dimly-stained matrix.

TABLE I—Continued

"Vegetative" or Trophozoite Stage—Iron Hematoxylin Stain—Continued				
	Entamoeba Histolytica	Entamoeba Coli	Endolimax Nana	Iodamoeba Butschlii
				Dientamoeba Fragilis
Intranuclear chromatin	No chromatin between karyosome and nuclear membrane.	Chromatin grains between karyosome and nuclear membrane.	No chromatin between karyosome and nuclear membrane.	No chromatin between karyosome and nuclear membrane.
Inclusions	Red blood-corpuscles. No bacteria unless degenerated.	No red blood-corpuscles. Many bacteria and other material.	No red blood-corpuscles. Many bacteria.	No red blood-corpuscles, bacteria.

Cystic Stage Iodine Smear Preparations				
Size in microns	6 to 20 $\mu$	10 to 33 $\mu$	5 to 14 $\mu$	5 to 20 $\mu$
Shape	Usually spherical	Usually spherical	Spherical, oval or ellipsoidal.	Irregular
Cytoplasm	Bright greenish yellow	Yellowish-brown	Pale green, with numerous refractile vacuoles	Yellowish-green
Glycogen mass	Diffuse and reddish brown.	Dark brown and indefinite central mass with indistinct border.	Usually absent, brownish and either diffuse or defined.	Usually present, dark brown, and sharply outlined.
Nuclei	1 to 4. Minute central karyosome very refractive. Nuclear membrane beaded and refractive.	1 to 8 or more. Nuclear membrane refractive and granular. Karyosome eccentric.	1 to 4 Indistinct	Indistinct. One usually present.



TABLE I—Continued

	Entamoeba Histolytica	Entamoeba Coli	Endolimax Nana	Iodamoeba Bütschli	Dientamoeba Fragilis
Cystic Stage. Iron Hematoxylin Stain					
Size in microns	6 to 20 $\mu$	10 to 33 $\mu$	5 to 14 $\mu$	5 to 20 $\mu$	No cysts have been found
Shape	Usually spherical	Spherical	Oval or ellipsoidal	Irregular	
Cytoplasm	Alveolar, often vacuolated.	Granular and vacuolated	Vacuolated with chromatin granules.	Vacuolated; large glycogen vacuole usually present.	
Chromatoidal bodies	Bar, oval or thick rod-like masses with rounded ends.	Filamentous, thread-like or splinter-like, with square or pointed ends.	Small, spherical or bacilliform, often in a vacuole.	Usually absent; when present, small, round or granular.	
Nuclei	1 to 4; delicate membrane lined with minute chromatin granules; karyosome minute central dot.	1 to 8 or more; thick nuclear membrane lined with large dots of chromatin or irregular masses; karyosome eccentrically placed and large.	1 to 4; nuclear membrane indistinct; karyosome in a single or divided mass on or near nuclear membrane.	1, rarely 2; nuclear membrane very thin, often indistinct; karyosome placed centrally or laterally and surrounded by large granules.	

are reached.<sup>3</sup> Likewise, the incidence of acute dysenteric manifestations of the disease diminish as the cooler climates are reached. In the United States, Craig estimates that from 5 to 10 per cent of the population are infected. This estimated incidence is based on survey data which was obtained from fecal examinations alone, in many instances from single stool examinations, and if multiple examinations of fecal specimens from each individual surveyed and other methods of diagnosis (complement fixation and cultural methods) had been employed, the incidence would probably be higher. It must be recognized that the incidence of infection will vary with the locality. The occurrence of the Chicago epidemic in 1933, during which over 800 cases with 40 deaths were observed, has brought about the realization that under suitable conditions even the most severe manifestations of amebiasis may occur in sites far removed from the tropics. Yet Borland<sup>8</sup> points out that the study of protozoal diseases has not yet aroused the interest that it should. This lack of interest he believes is due to 4 factors:

1. Failure to recognize the nontropical incidence of the infections.
2. Failure to realize that symptoms other than diarrhea may result from the infection.
3. The difficulty in finding and recognizing the various organisms.
4. The failure to recognize the necessity of examining material which has not been rendered unfit for examination by improper collection or previous use of drugs.

**Pathology**—Faust,<sup>4</sup> in a recent discussion of the problem of amebiasis, calls attention to several facts that must be considered in the evaluation of the disease. The first is that the *Entamoeba histolytica* usually invades the large bowel or rarely the terminal few inches of the ileum. The usual sites where the

preponderance of lesions are found are in the cecum, the rectum, and sigmoid. The involvement of the bowel may be quite superficial or may be quite extensive, with burrowing through all the coats of the bowel. From the primary sites of invasion, secondary foci may occur. Thus, from a primary site in the cecum, amebae may be planted lower in the bowel by transmission in the fecal stream; likewise, the organisms may be transmitted to the liver by way of the mesenteric venules. From the liver, by direct extension, the organisms may get into the lungs. Possibly some of the organisms may be transmitted by way of the lymphatics directly to the lungs and thence to other sites, as the brain, spleen, urinary tract, the lymphatics and skin. With the fundamental concept of amebiasis in mind, the symptomatology of amebiasis will vary roughly with the site and degree of involvement of the various tissues. Cecal amebiasis is not as likely to produce diarrhea as rectal amebiasis. Indeed, Craig and others have demonstrated that severe degrees of intestinal ulceration may occur without any symptoms.

**The Carrier Problem**—The high incidence of amebiasis in the general population (5 to 10 per cent) in the United States creates a serious public health menace. Craig denies the existence of such a thing as a "healthy carrier," since he and others have shown that pathological lesions practically always exist in individuals infected, even though they do not present symptoms. In his experience, about 65 per cent of individuals harboring the parasite either have had or will have symptoms. Approximately 35 per cent of the population harboring the parasite may not present any symptoms. All of this group of asymptomatic or mildly complaining individuals should be thoroughly treated as a preventive pub-

lic health measure, and to prevent serious subsequent developments, such as liver abscess. This concept of the carrier would indicate that a large number of these patients suffer from mild symptoms referable to the gastrointestinal tract. In this group, however, treatment should remove these symptoms. Paulson and Andrews,<sup>5</sup> and Howard<sup>6</sup> do not find removal of parasites to be of primary importance in relieving abdominal symptoms which may be present coincidentally with the parasites. Despite this unfavorable response, however, these investigators advise antiamebic therapy from the public health standpoint, and for the possibility of the occurrence of later serious complications.

**Diagnosis**—The diagnosis of amebiasis depends upon the demonstration of the *Entamoeba histolytica* in discharges or tissues of the suspected case. To this end, there can be no substitute for a thorough examination of a suitable fecal specimen by someone competent to recognize the parasite and differentiate it from the nonpathogenic species.

In making stool examinations, it must be remembered that trophozoites occur in liquid or semiformed stools, and that precysts and cysts are to be found in formed stools. Liquid material must be examined immediately lest the trophozoites deteriorate to such an extent as to be unrecognizable. Formed stools should be freshly passed also, but the recognizable characteristics of cystic forms of the parasites will persist for much longer periods of time. Where immediate examination of formed material is impossible, Borland<sup>4</sup> recommends the use of 5 per cent formalin as a preservative, since he has kept cysts for as long as 2 years without deterioration by means of this procedure. Feces frequently are rendered unfit for examination by the therapeutic use of mineral oil, bismuth or barium.

In the case of mineral oil, the refractile oil globules render the finding of cysts almost impossible, and barium and bismuth greatly reduce the number of cysts in the stool.

The most frequent site of invasion of the tissues is high in the colon near the cecum, and near this site the number of organisms will be highest, diminishing as the fecal stream approaches the anus. Hence, it is always wise to examine at least 1 stool after a saline purge, or as Paulson and Andrews<sup>5</sup> recommend, after lavage of the sigmoid stream, through the sigmoidoscope. No case should be considered negative unless at least 6 stools have been examined on successive days, one of which should be collected after a saline purgative. The actual microscopic examination of feces should be done by *direct microscopy* and after concentration. Faust and his associates recently developed the *zinc sulfate centrifugal flotation method*, which is reported to be vastly superior to the older methods of enrichment. Likewise, both stained and unstained specimens must be examined. D'Antoni's<sup>2</sup> standardized *iodine stain* is that most generally useful. The morphological characters of the various amebae are given in Table I.

The use of cultural methods will be found to be useful in many cases.

Craig has described a *complement-fixation test* which is specific for amebiasis. This test is not recommended by its author as a substitute for accurately performed fecal examinations, but is useful where such competent examinations are impossible to obtain, and in watching the response to therapy.

The usefulness of the *sigmoidoscope* in the diagnosis of amebiasis is limited. The morphological characteristics of the ulcerations seen in the rectum or sigmoid are not typical enough to be a substitute for the identification of the organ-

ism itself. Its main usefulness lies in increasing the yield of organisms and determining the presence of ulcerative lesions within its reach. When ulcerations are found, material obtained from the cavity of the ulcer should be examined immediately. A procedure which has been found to be helpful in some instances is to obtain material from the ulcerative lesion on cotton swabs and shake this out in a 3 to 4 cc. of warm physiologic saline solution and prepare slides from this emulsion for microscopic examination.

*Roentgen ray examination* of the colon in cases of amebiasis cannot be considered specific. Many investigators have noted the fine feathering of the outline of the colon and distortion of the mucosal pattern in the rather acute cases. In more chronic cases, the shortening, thickening, and angulation of the colon may be determined. At times, filling defects are observed. There are, according to Ikeda, no pathogenic x-ray signs of amebic involvement of the colon. Such examination is not to be neglected, since it furnishes good evidence of the degree of involvement and is perhaps an aid in prognosis.

The diagnosis of *amebic abscess of the liver* depends upon the demonstration of signs and symptoms of hepatic involvement together with the demonstration of the presence of *Entamoeba histolytica* by fecal examination or complement-fixation test. X-ray examination is particularly useful in demonstration of the elevation of the right diaphragm, which commonly occurs. It must be remembered that cases having a liver abscess need not have had a previous history of dysentery. In the experience of Ochsner and DeBakey, no history of dysentery was present in 40 per cent of the cases. Indeed, 60 per cent of the cases failed to show amebae in stool examinations.

The diagnosis of amebiasis in other organs or tissues requires the demonstration of the organism from the suspected lesion, either by culture or by microscopy. It is wise to remember that the *Entamoeba histolytica* does not encyst in the tissues.

**Treatment**—The drugs which have proven most useful in the treatment of amebiasis are *emetine hydrochloride*, *chiniofon*, *vioform* and *carbarsone*.

For the treatment of *acute amebic dysentery*, Craig recommends the administration of 1 grain (0.065 Gm.) of *emetine hydrochloride* subcutaneously each day until the dysenteric symptoms subside and the stools are semiformal or formed. Emetine given in this fashion should never be continued for longer than 12 days. In most cases, there is a prompt subsidence of the symptoms after the first 4 or 5 injections. Toxic symptoms should be a sign to stop the emetine. The signs of intolerance are great muscular weakness, increased diarrhea, nausea and vomiting, myocardial failure, and neuritis. The drug should never be used intravenously. After the acute symptoms have abated, then amebicidal drugs, such as *chiniofon*, *vioform*, and *carbarsone* should be used, as described below.

*Chiniofon* (sodium-iodoxyquinoline-sulfonate) contains 26 to 28 per cent iodine and its amebicidal properties depend upon its iodine content. This drug probably enjoys the widest degree of popularity and has proven highly satisfactory for 20 years. It has low toxicity and has very high amebicidal properties. Craig recommends this as the drug of choice in the therapy of amebiasis. It is usually supplied as enteric-coated pills or tablets of 4 grains (0.26 Gm.). The dose is 3 pills, 12 grains (0.75 Gm.), 3 times a day after meals for from 8 to 10 days. In full dosage, the drug may cause

excessive diarrhea, hence it is wise usually to start with 2 pills 3 times a day, and increase the dose to 3 pills. The diarrhea produced by the drug is beneficial, since it tends to wash out the organisms that are free in the lumen of the intestine. This drug is usually the most satisfactory one in the treatment of carriers and individuals having mild diarrheal symptoms.

**Vioform** (iodochloroxyquinoline) contains 37.5 to 41.5 per cent iodine upon which its therapeutic activity depends. It is usually administered in the form of gelatin capsules each of which contains 4 grains (0.26 Gm.), 3 times a day after meals. It is perhaps slightly more toxic than chiniofon, but such toxic action is slight. A full course of vioform consists of 4 grains (0.26 Gm.), 3 times a day for 10 days. The same dosage is usually repeated after a rest of 10 days.

**Carbarsone** (p-carbamido-phenylarsonic acid) contains 28.85 per cent arsenic. Rarely do toxic symptoms, which are colic, diarrhea, puffiness of the eyes, and skin eruptions, appear. The drug is marketed in gelatin capsules containing 4 grains (0.26 Gm.). The dose recommended is 1 capsule twice daily for 10 days. If the amebae have not disappeared from stools, the same dosage is repeated after a rest of 10 days.

In the treatment of *symptomless carriers* emetine should not be used. **Chiniofon** is recommended as the drug of choice. If this drug fails to eliminate the parasite, one of the other drugs, either **vioform** or **carbarsone**, should be used. Where nonpathogenic amebae are found in stools of individuals who have intestinal symptoms, amebicidal therapy should be tried.

The treatment of *hepatic abscess* is primarily **surgical**. It should be remembered, however, that presuppurative abscesses may be aborted by the use of **emetine hydrochloride** (Rogers). Regardless of whether or not surgery is to be done, the patient should be given a preliminary course of emetine therapy before any procedure. The usual procedure is to administer emetine hydrochloride 1 grain (0.065 Gm.), subcutaneously each day for a period not to exceed 12 days before any attempt to drain the abscess is made. Ochsner and DeBakey found that the incidence of recovery from amebic abscess of the liver was about 40 per cent in untreated cases and 90 per cent to 100 per cent in cases treated with emetine. A combination of **emetine therapy and repeated aspiration** is the procedure of choice. Open drainage should not be done unless secondary infection is present.

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## CHRONIC ULCERATIVE COLITIS

By J. ARNOLD BARGEN, B.S., M.D., M.S.

**Introduction**—That little new material has been added to previous knowledge in the past 2 years is indicated by several splendid reviews of the subject by Willard,<sup>7</sup> Goldsmith,<sup>8</sup> Chopra and Ray,<sup>9</sup> Feder,<sup>10</sup> Kopelowitz,<sup>11</sup> and Cartwright.<sup>12</sup> These men have reviewed the current theories on etiology, discussed the clinical course of the disease, stressed

the current therapeutic management, but have failed to mention the fact that chronic ulcerative colitis as it is known today is probably a syndrome consisting of numerous disease entities. This phase of the subject will be considered in this review.

**Etiology**—The literature of this biennium is replete with reviews on the

theories of etiology but is lacking in new facts. Willard<sup>7</sup> considered the etiologic relation of *Shigella dysenteriae* (*bacillus dysenteriae*), the *Bacterium necrophorum*,<sup>13-16</sup> streptococci, virus infection, allergy, deficiency states, muscle spasm,<sup>17</sup> and psychogenic factors to chronic ulcerative colitis. He also emphasized the importance of predisposing factors, such as upper respiratory infections. Chopra and Ray<sup>9</sup> added to these etiologic factors the importance of body mechanics and stressed the importance of streptococcal infection. They mentioned 4 main types of the disease: (1) The infective; (2) the allergic, (3) the neurasthenic, and (4) that associated with avitaminosis. The question of the relation of bacillary dysentery to chronic ulcerative colitis seems to have been fairly well settled by the review by Brown and the writer.<sup>18</sup> It was found 15 years after an epidemic in which 140 cases were studied that chronic ulcerative colitis had developed in only 1 of the 140 cases. Kopelowitz<sup>11</sup> suggested the possible relation of endocrine disturbances to chronic ulcerative colitis and again mentioned calcium and parathyroid deficiencies. He presented an especially well organized review of the subject. Feder,<sup>10</sup> in his analysis of 88 cases, lent substantial evidence to the diplostreptococcal origin.

Reed<sup>19</sup> found that the value obtained from vaccine therapy is largely influenced by psychologic factors, since the disease occurs "especially in neurotic, nervous, and somewhat hyperthyroid patients." Such experience is in entire disagreement with that of all other workers, for there is no evidence that patients who have ulcerative colitis are hyperthyroid. Although he decried the streptococcal theory of etiology, it is noteworthy that the streptococcus was isolated from the lesions of 19 of his 35 patients. He offered suggestions for and against

a bacterial cause of the disease; he listed in favor of a bacterial origin the fever which these patients have, the association of the disease with other bacterial infections, the isolation of bacteria of probable pathogenic qualities; favorable reports from the use of "complete" vaccines; increased sedimentation rates, and the nature of the pathologic changes. Against a bacterial cause he listed the noncontagiousness of the disease, the lack of characteristic reactions in the blood, the great variety of bacteria suspected, the difference in bacteriologic findings in different geographic sections, the frequent tendency to remission, the frequent ineffectualness of vaccine, the common disagreement of careful bacteriologic findings in the same section of the country, the postulation by proponents of each bacterium, that innumerable bacteriologic analyses are necessary to rule out the particular bacterium being considered. Most of these shortcomings can be summed up by the fact that the intestinal contents abound in bacteria too numerous to mention and unless special bacteriologic technic is employed the offending organism may not be found.

Rachet and Arnous<sup>20</sup> have formulated the conception of the inception of the disease as a sensitivity to a specific streptococcus, and Cartwright<sup>12</sup> again stressed the importance of streptococci. In a discussion of his paper Graham<sup>21</sup> emphasized the fact that he and his associates have isolated the diplostreptococcus in 75 per cent of their cases and have had excellent results with the use of serum and vaccine in treatment. Dack and his associates<sup>13-16</sup> continued to feel that *Bacterium necrophorum* plays a rôle in the etiology. They stated that this organism is similar to, or identical with, the *Bacteroides funduliformis*. It is generally recognized that the latter organism occurs in various types of perforative, sep-

tic intestinal lesions, particularly in perforative carcinomas of the distal portion of the large intestine.

Paulson<sup>22</sup> attempted to approach the study of etiology from the standpoint of a virus in the discharge from the bowel which is similar to that found in lymphogranuloma venereum. So far no positive data for this are at hand.

The work of Lum and Porter,<sup>23</sup> who have produced ulcerations in experimental animals as a result of trauma and muscle spasm, is worthy of mention, but it must be remembered that this type of ulceration when present is a secondary effect and occurs in a small percentage of patients who have real ulcerative colitis.

Wittkower,<sup>24</sup> von Hoesslin,<sup>25</sup> and Brown, Preu and Sullivan<sup>26</sup> again have stressed the importance of the psychic phase. The first of these authors concluded that "no uniform personality type" can be established as susceptible to the disease.

Lerner and Rapaport<sup>27</sup> stressed the fact that the deficiency syndrome does not manifest itself with any obvious clinical evidence until late in the disease, but they found a subclinical deficiency of vitamin A in 41 per cent of their cases.

Fradkin<sup>28</sup> reported a case in which the diagnosis of ulcerative colitis was made 28 years before *Entamoeba histolytica* was recovered from the lesions; he emphasized again the great importance of proper classification and differentiation.

**Pathologic Features**—The tendency for students of the problem to discuss all kinds of ulcerative colitis as a single entity and to consider the mucosal infection as the basic one still exists.

Kahler<sup>29</sup> recognized the diffuse nature of the intestinal infection in ulcerative colitis and of the lesion of the mucous membrane but continued to dwell on the existence of the large secondary ulcers;

thus he gave the impression that these were primary phenomena.

Stafford<sup>30</sup> compared the lesions in 10 cases of regional ileitis with those in 3 cases of lymphogranuloma venereum; he spoke of the latter as ulcerative colitis, and intimated that all of these lesions may be due to some form of virus infection.

Cabot<sup>31</sup> again called attention to the fact that chronic ulcerative colitis may spread proximally to involve long stretches of ileum. Bases<sup>32</sup> reported a case of localized acute phlegmonous colitis.

There is much merit in all these reports but unless the authors specifically designate the form of colitis to which they refer and unless they distinguish it from other types, the confusion now existing in regard to classification of forms of ulcerative colitis will only be increased.

**Complications**—The anal and rectal conditions are among the most distressing complications of chronic ulcerative colitis. Smith and Jackman<sup>33</sup> have dealt with *fistulas*, *extensive anal ulceration* and *anal and rectal contractions* in a most practical manner; they urged the avoidance of surgical interference during the active stages of the disease. Taube<sup>34</sup> reported *acute appendicitis* associated with chronic ulcerative colitis in 1 case; although this apparently has been reported only rarely, a number of such cases has been observed at The Mayo Clinic. The physician who cares for these patients must be ever alert for this happening. The sequel of *carcinoma* among the younger patients who have chronic ulcerative colitis has been observed frequently, <sup>35, 36</sup> and Matzner and Schaefer<sup>37</sup> reported the case of a man 29 years of age. *Vitamin deficiency* as a late complication has been reported by Clark,<sup>38</sup> and *infantilism* by Davidson<sup>39</sup>

and Kindschi.<sup>40</sup> At The Mayo Clinic a number of cases has been observed of infantilism which was a late complication when the disease had attacked children severely in the first decade of life. Schemensky<sup>41</sup> has attempted to explain the typical *blood picture* of chronic ulcerative colitis on the basis of an interference with the blood-forming mechanism.<sup>42</sup> It is difficult to understand why frank hepatic insufficiency does not occur more commonly in association with chronic ulcerative colitis. It probably occurs rather commonly in subclinical states, but only 4 cases of *chronic jaundice* were reported by Comfort, Morlock, and the writer.<sup>43</sup>

Another condition observed more and more commonly in cases of long standing is "*clubbed fingers*."<sup>44</sup>

**Clinical Course**—As knowledge concerning any human malady accumulates, it often becomes apparent that many disease entities have been classed under 1 designation. It has been so with diseases of the lungs, with diseases of the kidneys and of many other organs. Only recently has this fact become apparent as far as the syndrome chronic ulcerative colitis is concerned. It has been shown that there is a streptococcal ulcerative colitis<sup>45, 46, 47, 48</sup> (type 1), a tuberculous ulcerative colitis (type 4), an amebic ulcerative colitis (type 5), a deficiency state with ulcerative colitis (type 6), an ulcerative colitis associated with lymphogranuloma venereum (type 7), and a group of cases of ulcerative colitis still remains in which the nature and etiology have not been understood so far and which have therefore not been properly classified. The writer and his associates<sup>46, 48, 49</sup> have designated these as ulcerative colitis of types 2 and 3. In these groups it has been possible to place the cases of bacillary dysentery, because their nature is rather bizarre and classi-

fication is not at all clear. Perhaps the etiologic factor in each of these 2 groups is the same, but they have been separated in this way because in ulcerative colitis, type 2, at present the diagnosis depends on the appearance of the lesion on roentgenologic study, for the lesions in these cases involve segments of bowel above the sigmoidoscopic field. Type 3 includes cases in which ulcerative disease can be visualized through the proctoscope, but the lesions are different from those seen in the streptococcal group (type 1); and this difference in appearance makes it possible to distinguish the cases from those of the streptococcal variety. It remains for students of the future to designate the nature of these cases. These suggestions have been confirmed, although at times unwittingly, by such reviews as those of Willard,<sup>7</sup> Chopra and Ray,<sup>9</sup> Kopelowitz,<sup>11</sup> Feder,<sup>10</sup> and Reed.<sup>19</sup> Cullinan<sup>50</sup> has attempted to establish relationship with the so-called catarrhal, simple, and idiopathic forms of ulcerative colitis. Such relationship, however, has rarely been found to exist by those who have seen large series of cases of chronic ulcerative colitis.

In general, cases of chronic ulcerative colitis of the streptococcal variety (type 1) can be divided into 8 groups according to their clinical course. Table II<sup>46</sup> illustrates this well.

**Prognosis**—This phase of the subject has been set forth in an excellent review by Willard, Pessel, Hundley and Bockus.<sup>51</sup> They stated that the mortality rate ranges from 10 to 40 per cent. The results depend on the type of disease, the time the cases have been followed, and the incidence of operation. They emphasized that results depend on a multiplicity of therapeutic measures, rather than on a single therapeutic measure. The best results are achieved in those cases in which a chronic relapsing course



TABLE II  
(Bargen, Jackman and Kerr<sup>46</sup>)  
MANNER OF PROGRESSION OF CHRONIC ULCERATIVE COLITIS

Course*	Age at Onset Males					Age at Onset Females				
	0-9	10-19	20-29	30-74	Total	0-9	10-19	20-29	30-74	Total
Mild throughout entire course		10	28	48	86	2	4	31	34	71
Intermittent with declining severity	4	21	23	41	89	2	6	13	29	50
Septic course with complete recovery		2	11	10	23	1	7	9	4	21
Constant without remission		4	7	11	22		9	18	20	47
Slowly progressive without remission	4	7	32	46	89	4	6	24	20	54
Intermittent with progressive severity. . . . .	7	17	55	49	128	1	30	47	40	118
Insidious onset with slow progression, changing to fulminating course and ending fatally. . .	4	11	8	18	41	3	2	5	1	11
Fulminating course throughout, ending fatally. . . . .		2	5	6	13		3		5	8

\* These descriptive phrases concern the historical data, as obtained from patients, before admission to the clinic.

occurs. The highest mortality rate appears in the cases in which the course is fulminating. The extent of involvement, as depicted roentgenologically, is not a reliable prognostic sign. The immediate postoperative mortality rate is 42 per cent and the death rate in the surgical cases is 73 per cent. Their review is based on a critical analysis of 66 cases of their own and an intensive review of the literature.

Another comprehensive review of this phase of the subject came from Buzzard, Richardson and Turner,<sup>52</sup> from St. Thomas's Hospital, London. Their report is based on the study of 120 patients observed in the years 1927 to 1936, inclusive; 116 were traced; 35 had died from 2 to 12 years after the first observation, 29 while in the hospital, and 6 while under their care outside, a mortality rate of 30.2 per cent. Twenty per cent of all the patients died in less than

2 years from the time of the first observation; 8 per cent in less than 4 months. No treatment helped in the fulminating cases. Sixty-eight patients were still alive; 12 of these were normal in every way. Twenty-six per cent of those who survived, and did not have an operation, were well enough to earn their living and carry on all normal and usual functions. Mucous colitis did not precede the ulcerative colitis in these cases. Worry was found to be the chief cause of relapse among their patients. These authors stressed the importance of temperament, and stated that persons who come to terms with their complaint undoubtedly do well, but that worriers do not. They stated, "A few years ago the well-recognized difficulties in the management of chronic ulcerative colitis had led to a wave of enthusiasm for surgical methods. Encouraging reports by individuals raised hopes which wider experi-

ence has not justified." Perhaps their statement, that in a few cases "individual preference and the presence of the patient in a surgical ward led to surgical treatment, but the result would have been equally happy by medical treatment," is an overstatement. Eleven of their 23 patients who underwent operation died.

**Medical Treatment**—Cullinan,<sup>53</sup> in an excellent review of the subject, stated that "nearly all patients with ulcerative colitis, even when they appear almost moribund, will respond well to careful treatment." While this may seem to be a rather strong statement, its general meaning can be accepted.

The program of management should include those measures usually applied toward the control of any serious, destructive infection, *i. e.*, **rest** and **restful recreation, diet, supportive measures**, administration of **parenteral fluids** to the sicker individuals, **blood transfusions, serum, vaccine** and **chemotherapy, local applications** in the cases in which the lesions are limited to the distal segments of the large intestine or there is much anal and perianal damage, adequate administration of **vitamins**, and attention to the **counteraction of allergens** in that small group of cases in which allergic phenomena exist. These matters have been properly stressed by Jones.<sup>54</sup> The writer has emphasized repeatedly the importance of rest. In a rather philosophical discussion Mackie<sup>55</sup> gave nothing of importance with regard to treatment.

1. **Diet**—In another report Mackie<sup>56</sup> stressed the importance of the proper manipulation of the diet. Donald and Brown,<sup>57</sup> Streicher<sup>58</sup> and Bodkin<sup>59</sup> further stressed the importance of a well-balanced diet and the value of a **high protein diet** has been emphasized repeatedly. The **raw apple diet** as a

supportive measure has been brought forth again by Cullinan.<sup>53</sup>

2. **Serum and Vaccine**—Woolf,<sup>60</sup> Streicher,<sup>58</sup> Feder,<sup>10</sup> Levin and Shushan,<sup>61</sup> Willard,<sup>7</sup> Schlicke and Barger,<sup>62, 63</sup> Graham,<sup>21</sup> Cartwright,<sup>12</sup> Miller,<sup>64</sup> and many others have used the antistreptococcus serums and vaccines with good result.

3. **Liver Extract and Histidine**—Crude liver extract has been used for years at The Mayo Clinic to combat vitamin deficiency, liver damage, and as a supportive measure. Cheney<sup>47, 65</sup> advocated the use of a highly concentrated liver extract, such as **reticulogen**. An analysis of his cases revealed, however, that he was treating a great variety of intestinal conditions, under the designation of chronic ulcerative colitis, by what was apparently a rather empiric form of treatment.

Histidine hydrochloride, 1 dram (4 cc.) of a 5 per cent solution administered subcutaneously, has apparently been of value in selected cases. Bercovitz<sup>66</sup> has had good results with this substance in a few cases.

4. **Vitamins**—Mackie and Eddy<sup>67</sup> stressed the clinical value of determining quantitatively the vitamins in the blood of these patients. Vitamin therapy is then applied in accordance with results of the tests. Elmy<sup>68</sup> has had good results with the use of **ascorbic acid, citrin** and **fruit**. Willard<sup>7</sup> emphasized, particularly, the importance of **vitamins A, B, C, D, and K**. When the prothrombin in the circulating blood is depleted and the patient has been deprived of adequate vitamin C, the hemorrhagic tendencies can be reduced in some cases by the administration of these vitamins.

5. **Topical Applications**—Best,<sup>69</sup> Gainsborough,<sup>70</sup> and Manville<sup>71</sup> have had good results in cases of mild disease from the instillation of **cod-liver**

oil into the rectum and Eyerly and Breuhaus<sup>72</sup> have seen benefit from the use of *aluminum hydroxide* and *kaolin*. The cod-liver oil should be warm and 2 to 4 ounces (60 to 120 cc.) should be instilled daily.

6. **Sulfonamide Drugs**—The most useful drug exhibiting the least signs of toxicity has been *neprontosil*, given after the methods of Brown, Herrell, and the writer;<sup>73</sup> 50 to 75 grains (3.2 to 4.8 Gms.) is given in divided doses each 24 hours for about 2 weeks, then the patient is allowed a rest of a week, and the course is repeated. The hemoglobin and leukocytes should be watched carefully when any of this group of drugs is given and the length of treatment gauged by the blood findings and the concentration of the drug in the blood. Collins<sup>74, 75</sup> has obtained good results with the use of *sulfanilamide* by mouth and by rectum. At The Clinic the use of this drug has been discontinued because of toxic reactions. Bercovitz<sup>66</sup> and many others more recently also have advocated the use of *neprontosil*.

7. **General Considerations** — Some physicians are most emphatic about the medical treatment of "chronic ulcerative colitis." Woolf<sup>60</sup> stated that the treatment should be entirely medical. In Streicher's<sup>58</sup> 217 cases *surgical intervention* was resorted to in only 3 instances. Only 3 of Feder's<sup>10</sup> 88 patients were operated on; 2 died after appendicostomy and ileostomy, respectively, and a third who was subjected to cecostomy was unimproved. Fifty-seven of his patients were improved or "cured" and 10 died under his medical regimen. Goldsmith's<sup>8</sup> medical regimen resulted in excellent control of most cases but with a mortality of 9.4 per cent. Reed's<sup>19</sup> statement that "some aggravated, almost ma-

lignant cases clear up with treatment" is difficult to interpret.

Measures of *prevention of relapses* are considered by several workers. Bercovitz<sup>66</sup> stressed the importance of *removing foci of infection*; Kunstler,<sup>76</sup> the *avoidance of upper respiratory infections*; and Felsen<sup>76a</sup> considered the *prevention of acute bacillary dysentery* important. In younger women, the question of *pregnancy* in association with chronic ulcerative colitis often arises. This problem has been dealt with in an article by Bargaen, Nunez and Mussey.<sup>77, 78</sup>

**Surgical Treatment**—About 15 years ago surgical intervention was advocated as a treatment for chronic ulcerative colitis; the nature or type of disease for which it might be of particular value was not specified. At that time, all forms of chronic ulcerative colitis that were not tuberculous or amebic were thought to be of a common variety, excluding, of course, those forms of colitis seen in association with various toxic states such as uremia. It soon became apparent that surgical treatment was not the treatment for the patients who were violently ill with ulcerative colitis; the surgical procedures in such cases usually consisted of ileostomy, or possibly other even more major procedures. Not only were the end-results not satisfactory, but the mortality rate was forbiddingly high. Such exploits as appendicostomy, cecostomy, and colostomy, moreover, usually fell far short of their desired goal. Surgical intervention consequently gradually fell into disrepute for intractable chronic ulcerative colitis. It found its place in the treatment of complications and of sequelae of this condition. When the active phase of the disease had subsided and left uncontrollable intestinal strictures, extensive perianal abscesses and fistulas, slowly perforating lesions, oc-

casional massive hemorrhages, extensive secondary polyposis, neoplastic change, or severe secondary arthritis, *ileostomy* and *colectomy* could be done with reasonable safety and with satisfactory end-results. This is and should be the status of surgical procedures today in the streptococcal (type 1) variety of ulcerative colitis. On the other hand, in *type 2* (the regional) *ulcerative colitis*, *ileo-colostomy* and *segmental resection* are today the treatment of choice. In type 3, the group of cases of ulcerative colitis of unknown cause and nature, a satisfactory treatment has not been found as yet. The status of ileostomy in this type of colitis is much the same as that in all cases, no matter what type of ulcerative colitis it is.

True enough, a few articles have appeared in the literature in which operation is advocated without regard to the classification of the disease. Cave<sup>79-81</sup> stated that "many patients have been lost because radical surgical measures were denied them. In his report on 257 cases, however, the medical mortality rate was 6.2 per cent and the surgical mortality rate 22.5 per cent; in 158 of these cases in which treatment was given at the Roosevelt Hospital under very well-controlled conditions, the medical mortality rate was 3.7 per cent and the surgical mortality rate 18.5 per cent; for the other 99 patients from various other hospitals in New York the medical mortality rate was 10.1 per cent and the surgical mortality rate 30.8 per cent. Of the 5 surgical deaths in the Roosevelt Hospital group, 4 followed ileostomy and 1 subtotal colectomy. The operations performed included ileostomy 19 times, ileosigmoidostomy 3 times, colostomy 3 times, total colectomy 3 times, and subtotal colectomy 3 times. Cave did not mention the type of case for which these surgical measures were undertaken. It

seems obvious that ileosigmoidostomy and colostomy were not for the streptococcal form (type 1) of ulcerative colitis. Cave and Mackie,<sup>82</sup> speaking of ulcerative colitis in general, stated, moreover, that "it seems unusual that relatively little has been written about this disorder."

Cattell<sup>83</sup> emphasized the fact that "chronic ulcerative colitis is primarily a medical problem," and that medical

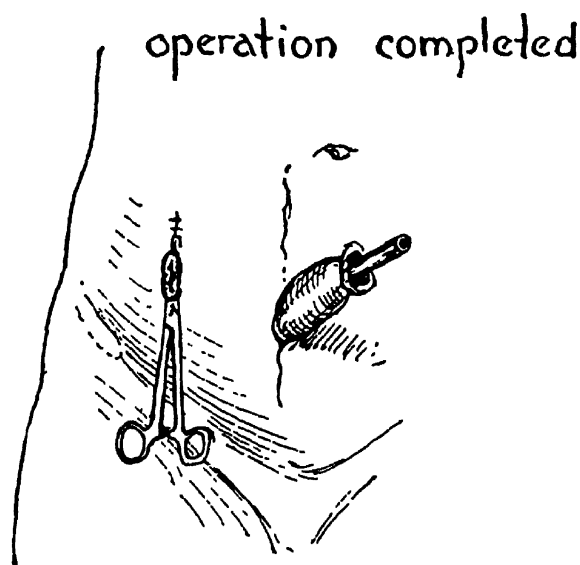


Fig. 1—Ileostomy after method of Cattell.  
(R. B. Cattell: S. Clin. North America.)

management offers satisfactory relief in 75 per cent of the milder cases. He considered "ileostomy the price that some patients must pay for life" but even so it is done with a 22 per cent mortality rate. If the patient, however, is brought to the stage at which colectomy becomes feasible, *colectomy* then can be done with a 9 per cent mortality rate. He advocated performing this type of operation in stages and reported that 21 patients have survived complete colectomy. He has introduced a type of *ileostomy* which should have much merit (Fig. 1<sup>84</sup>). Rankin<sup>85</sup> is in general agreement with Cattell.

Jones<sup>86</sup> advocated *colostomy* instead of ileostomy whenever possible. In ex-

perience at The Mayo Clinic this has been an unsatisfactory operation, for every patient who was subjected to operation in the earlier years returned later with ulcerative colitis in the bowel prox-

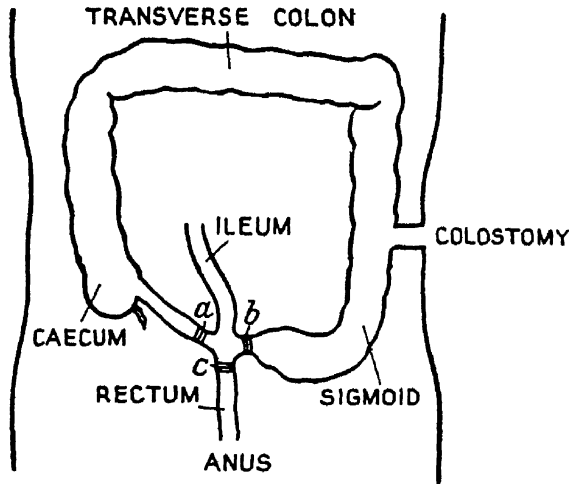


Fig. 2—Scheme of ileosigmoidostomy. In first operation bowel is ligated at *a* and *b*. In second, these ligatures are removed and ligature is applied at *c*. (Gaha: Lancet.)

imal to the colonic stoma. Campbell<sup>87</sup> reported a case of *colectomy* for chronic ulcerative colitis with arthritis and a deficiency state. Hurst<sup>88</sup> reported the result in a case in which *segmental*

*colectomy* was done, apparently for ulcerative colitis type 2. Cushman and Kilgore<sup>89</sup> gave the only available report on *appendicostomy*; their 5 patients received intestinal irrigations through the stoma later with satisfactory results. Sedgley,<sup>90</sup> on the other hand, advocated only *ileostomy*. A unique report came from Gaha,<sup>91</sup> of Tasmania. He performed the first *colostomy* in the descending colon and *ileosigmoidostomy*, and then *ligated the ileum distal to and the sigmoid proximal to the anastomosis*. Later, he removed these ligatures and tied off another segment of the bowel (Fig. 2). It seems doubtful whether the patients with the types of ulcerative colitis seen in America could survive such procedures.

If this summary does no more than again call attention to the serious nature of these maladies, the many unknown factors about the cause of some forms of ulcerative colitis, and the importance of an approach to the problem by careful analysis of each case, it will be worth while.

## PANCREAS

By A. H. AARON, M.D.

In view of the fact that lesions of the pancreas are usually of such an acute nature or malignant in character, a review of the literature for the past year reveals a constant effort on the part of clinicians and surgeons to recognize lesions of this organ as early as possible by clinical and laboratory studies so that adequate therapy may be inaugurated. Many functional tests are proposed but at the present none seems satisfactory. This is due to the large margin of safety present in the pancreas as revealed by the work of Coffey, Mann and Boll-

man,<sup>92</sup> who demonstrated in animals that approximately one-fortieth of a normal pancreatic gland was able to supply by minute ducts an adequate amount of external secretion to carry on normal digestion in the gastrointestinal tract. It is evident, therefore, that any test of enzymatic concentration in the duodenal contents will only reveal diminished secretion when less than one-eighth of the gland is active.

### Functional Tests

Examination of the duodenal contents has been carried out by a new method by

Comfort and Osterberg<sup>93</sup> through the use of the double lumen tube. One tube kept the stomach empty by moderate suction and thus prevented contamination of the duodenal contents; from the other the contents of the duodenum was secured. They performed analyses of the pancreaticobiliary duodenal secretion following stimulation with intravenous secretin and subcutaneous mecholyl chloride. Their work was based on the fact that secretory activity of the pancreas may be stimulated by either humoral (secretin) or a neural (vagal) mechanism. They concluded that secretin and mecholyl chloride produced contrasting effects on the pancreatic secretion as indicated in Table III.

The increase in total value for these enzymes appeared to be due to a washing-out process in the case of secretin but was due to an active secretion of enzymes in the case of mecholyl chloride. The total value for lipase was likewise increased after each type of stimulant, but the increase was more prolonged after secretin than were the total values for amylase and trypsin. The significance of the different types of behavior is not clear. Stimulation with secretin demonstrated that the pancreas is capable of secreting a large volume of high alkaline juice. Stimulation with mecholylchloride, on the other hand, demonstrated that the pancreas is able to secrete a juice rich in enzymes. These studies emphasize the possibility for further investigating secretory activity of the pancreas.

Diamond and his associates<sup>94</sup> report as follows on studies of the pancreatic function and the technic of the collection of pancreatic enzymes as obtained by the double lumen gastroduodenal tube, the technic being discussed in detail; 22 cases were studied; 8 of them with pancreatic disturbances. Secretions are collected from the duodenum for 20 minutes

TABLE III

	Secretin	Mecholyl Chloride
Volume	A marked increase	Slight increase
pH	Increased values	No appreciable effect on pH values
Concentration of enzymes	Prolonged reduction	Prolonged increase of concentration of enzymes
Amylase	Increased value first 10 minutes	Prolonged increased values over 30 minutes
Trypsin	Increased values first 10 minutes	Prolonged increased values over 30 minutes
Lipase	Increased values	Increased values

as a base line. Then secretin is injected intravenously 0.5 mg. per kilogram and the volume of flow, concentration of bicarbonates, and enzymes are estimated separately. Normally there is an increase in all these elements. The reaction of the pancreas to secretin is as specific as that of the gastric cell to histamine. The increased output varies in proportion to body weight and normal values are established in this article. In the pathological state one or more of these functions may be impaired.

Pratt<sup>95</sup> emphasizes that increased values of diastase in the urine and lipase in the blood are of increasing diagnostic weight in the recognition of *acute pancreatic necrosis*, but calls attention to the fact that this is based on their frequent performance and a comparison of day-to-day figures on patients in whom this condition is suspected.

### Roentgenographic Observations

*Carcinoma of the pancreas* involves either the head, body or tail. Roentgenol-

ogy is assuming an important place in the diagnosis of carcinoma of the head of the pancreas by calling attention to the widening of the "C" angle of the duodenal curve. The x-rays also afford evidence of changes in the mucosal pattern of this part of the duodenum due to fixation and rigidity which may lead to the suspicion of an involvement of the head of the pancreas before widening of the "C" angle occurs.

Beling<sup>96</sup> describes a case of *calcification of the pancreas*. The diagnosis of this was made on the basis of the roentgenograms showing multiple calcific shadows.

Rockwern and Snively<sup>97</sup> report 2 cases of *pancreatic lithiasis* and state that the character of the pain in this condition may simulate biliary colic. During attacks the stool was voluminous, light tan, soft and oily. They call attention to the fact that the diagnosis may be made more frequently during life by careful roentgen examination of the abdomen before the administration of barium.

### Acute Pancreatitis

At the present moment the diagnosis of acute pancreatitis remains a clinical entity and calls forth all the skill of the physician in eliminating certain lesions that cause difficulty in differential diagnosis in acute abdominal emergencies, such as coronary occlusion, renal colic, perforations of the gastrointestinal tract, mesenteric thrombosis, tabetic crisis and other more infrequent conditions. Unfortunately, biliary tract disease is frequently associated with acute pancreatitis and it is here that the differential diagnosis is quite difficult. It has been said that with a biliary type of history, an acute attack where most of the symptoms and signs are to the left of the midline and posteriorly, one should suspect acute pancreatitis. Here enzymatic

concentrations are useless and urine amylase and blood lipase are frequently of little help as a guide when immediate surgery is being considered.

Morton<sup>98</sup> calls attention to the fact that acute pancreatitis of the edematous variety is a much less serious disease, especially in its milder forms, than the acute hemorrhagic type. He stresses that in 52 cases cited in the current literature only 3 deaths occurred in the first group, which is a mortality of 5.7 per cent, whereas in the severe forms there was a mortality of 60.8 per cent. He also calls attention to the fact that in those patients where it is possible to diagnose acute severe pancreatitis there will be a lower mortality rate by deferring surgery than by operating upon them as surgical emergencies. It is important to emphasize here the necessity of the physician and surgeon being most positive of the diagnosis. By refraining from surgery they may deny the patient a proper procedure for those conditions which are amenable to operative therapy, such as mesenteric thrombosis, intestinal obstruction, perforated viscus, etc. Judging from the inability to diagnose acute pancreatitis from symptoms and signs and limited laboratory facilities, it would seem at the present moment that intervention is advised when in doubt.

### Carcinoma

Levy and Lichtman<sup>99</sup> emphasize in their series the fact that when appreciable loss of weight, averaging 27 lb. (12.2 kg.), is observed in an individual in an absence of any other disease that regularly produces such a loss, *i. e.*, diabetes, hyperthyroidism, tuberculosis, anorexia nervosa, sprue or demonstrable malignant growth, an attempt should be made to exclude tumor of the pancreas.

Modern surgery at the present time offers certain advances that one may look

forward to more successful attack upon malignancy involving the pancreas if it is recognized at a stage when resection can be attempted.

### Lipocaic

In a review of the interesting subject of lipocaic, Dragsted<sup>100</sup> concludes as follows:

"1. The demonstration that lipocaic is an internal secretion of the pancreas depends on the recognition that the depancreatized dog, fed on a mixed diet, is not restored to a normal state by the adequate administration of insulin and pancreatic juice and that the remaining deficiency is corrected by the oral administration of pancreas but not by other organs.

"2. Extracts of pancreas have been prepared which are effective on oral and subcutaneous administration in daily doses of from 2 to 3½ ounces (60 to 100 Gm) of dried substance. Since the extracts are practically free from lecithin and choline, the former conclusion that the beneficial effect of pancreas feeding in depancreatized dogs cannot be accounted for on the basis of its content of these chemicals is confirmed.

"3 Two types of fatty infiltrations of the liver occur in both diabetes mellitus and pancreatic diabetes. One type is due to poor control of the diabetes by inadequate administration of insulin and is characterized by a normal or high concentration of the blood lipids and acidosis and is relieved by better insulin therapy. The second type is due to lipocaic deficiency and is characterized by a low concentration of the blood lipids, impaired liver function, decreased dextrose excretion and insulin sensitivity, and is relieved by lipocaic therapy but not by insulin.

"4. The occurrence of arteriosclerosis in depancreatized dogs is of greater in-

cidence than normal for this species. There is a possible relation of lipocaic to this complication in both pancreatic diabetes and diabetes mellitus."

That it may have an important clinical application is noted by Joslin, who feels that the enlargement of the liver may be due to extensive fatty infiltration in human diabetes mellitus.

Marble and his associates<sup>101</sup> and Grayzel<sup>102</sup> have treated a small group of patients in whom they believe the lipocaic factor was deficient, producing hepatomegalia in *juvenile diabetics*. They administered lipocaic by mouth and reported marked clinical improvement.

Its use in the treatment of diabetes is purely experimental. Stewart<sup>103</sup> advocated its employment in the treatment of *psoriasis*, as also did Clarke and his associates.<sup>104</sup>

In a report the Council of Pharmacy of the American Medical Association<sup>105</sup> states that in view of the experimental status of lipocaic, the merit of this product must await further evidence of its value, the preparation should not be used for routine practice, and at the present time no commercial preparation of lipocaic is on the market and its use must be considered as entirely in the experimental stage.

### Pancreatin

Childs and Dick<sup>106</sup> noted that in a case of *nontropical sprue* there existed a deficiency of some pancreatic factors as yet undetermined and that the greatest subjective improvement occurred after the use of pancreatic juice. When the use of dried pancreatic substance was administered Armour's pancreatin was a favorable adjunct, and had the advantage of being readily available and well tolerated. Pancreatin can be administered best in 2 heaping teaspoonful doses



prepared in the following manner: A small amount is put in a glass containing a little cold water and stirred to a paste, additional small amounts of pancreatin being added until the mixture has the consistency of thick cream, then more cold water may be added. If an attempt is made to put all the cold water in at once it is difficult to mix. This should be administered on an empty stomach 20 minutes before meals so that it will pass out of the stomach before hydrochloric acid can inactivate the greater part of the ferment. This product should be as fresh as possible by having the druggist secure a supply weekly from the manufacturer. Personal experience has shown that enteric coated tablets are inadequate, due to the small doses they contain.

The Council<sup>105</sup> also has reported on a product, "*depropanex*," which has

been advocated for the treatment of *angina pectoris* and *intermittent claudication*. So little work had been done with this, however, that its use must still be considered experimental in character and not for routine private practice.

### Rare Pancreatic Conditions

Among some of the more unusual conditions reported in the last year is that by Oppenheimer<sup>107</sup> of a case of *cystic fibrosis of the pancreas* caused by a true atresia of the pancreatic duct, resulting in a poor absorption of fat and a deficiency of vitamin A. Another unique case is that of Little's<sup>108</sup> describing *tuberculosis of the pancreas*. He suggests that the presence of this condition is to be suggested by persistent epigastric pain in a tuberculous diabetic patient.

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## SPRUE

By SEALE HARRIS, M.D.

**Etiology—Predisposing Factors of Sprue**—There seem to be many underlying or predisposing causes of sprue, the most important of which are infections or infestations of the gastrointestinal tract.

It seems probable that in all the predisposing causes of this disease there is damage to the duodenum, pancreas, and liver to the extent that duodenal, pancreatic and hepatic insufficiency are sequences.

A deficiency or absence of secretin, the hormone secreted by the duodenum and upper part of the jejunum, which activates the external secretions of the pancreas, may be an important factor in the etiology. Perhaps one of the reasons why large doses of dilute hydrochloric acid are helpful is because they activate the secretion of secretin in the duo-

denum and jejunum, which, in turn, stimulates the formation of steapsin, amylapsin and trypsin by the pancreas.

**Extrinsic and Intrinsic Factors in Sprue, Pellagra and Pernicious Anemia**—It seems probable that in sprue, as in pellagra, there are both extrinsic (exogenous) and intrinsic (endogenous) factors. The most important extrinsic factor in both sprue and pellagra seems to be food deficiency. In pellagra the essential deficiency is known to be nicotinic acid, the pellagra preventive factor in vitamin B, while in sprue the essential avitaminosis is not known, but thought by some to be another, as yet undiscovered, factor in the vitamin B complex.

**Intrinsic Factors**—The intrinsic factors in sprue seem to be duodenal, hepatic and pancreatic insufficiency; while in pellagra and pernicious anemia the

intrinsic factors appear to be gastric and hepatic insufficiency. In other words, when there is normal physiologic function of the duodenum, liver and pancreas, sprue does not occur; and when the stomach and liver function normally, pellagra and pernicious anemia cannot develop, even in cases of pronounced food deficiency. To express it in another way, the sprue victim has a damaged, poorly functioning duodenum, liver and pancreas, while the pellagrin's stomach and liver are damaged to such an extent that nicotinic acid cannot be stored up or utilized in the body.

**The Food Factor**—The food factor, a deficiency diet, certainly is much the same in the etiology of sprue and pellagra and to a less extent in pernicious anemia. The etiology of pernicious anemia is admittedly unknown. Ashford's theory of the monilia psilosis is not generally accepted as being the essential etiologic factor in sprue; and while a deficiency of nicotinic acid is the accepted cause of the symptoms of pellagra, all of the essential factors in the production of pellagra have not been discovered. It certainly seems that it would be advisable to continue investigations into the causes of sprue, pellagra and pernicious anemia until all the etiologic factors in each have been discovered.

**Common Pathology of Sprue, Pellagra and Pernicious Anemia**—Considering the pathology of sprue, pellagra and pernicious anemia, in the great majority of cases there is pronounced liver pathology—fatty degeneration usually—in all 3 of these diseases. Many writers have called attention to the fatty changes in the liver in sprue, pellagra and pernicious anemia.

Atrophy of the stomach may be seen in all 3 diseases; and subacidity and achlorhydria are evidences of damage to

the hydrochloric acid forming cells in the stomach in sprue, pellagra and pernicious anemia. Atrophy of the intestines may be seen in all 3 diseases. Likewise, there is marked similarity in the pathology of the lateral and posterior columns when there are cord changes in sprue, pellagra and pernicious anemia.

**Common Symptoms of Pellagra, Pernicious Anemia and Sprue**—The writer does not believe that pernicious anemia, pellagra and sprue are different manifestations of the same disease; on the contrary, it is evident that they are 3 separate and distinct disease entities. There are, however, symptoms which may be common to the 3 diseases, including all the gastrointestinal symptoms, nervous manifestations and macrocytic anemia.

Given a patient with achlorhydria, stomatitis, diarrhea, mental depression and the motor manifestations resulting from involvement of lateral and posterior columns of the spinal cord and severe anemia, it may be impossible to make a positive diagnosis of pernicious anemia, pellagra or sprue. The addition of a symmetrical, bilateral, pigmented, exfoliative erythematous dermatitis of the dorsal surfaces of the hands and feet in addition to symptoms which may be common to sprue and pernicious anemia enables the clinician to make a diagnosis of pellagra; while the large, fatty, fermenting, pasty, clay-colored stools in a patient with stomatitis, diarrhea and severe anemia may be the only pathognomonic difference between sprue and pernicious anemia.

The patient with stomatitis, diarrhea, mental, sensory and motor symptoms, and anemia without skin lesions who resides in a community in which pellagra exists would be regarded as a probable pellagrin. Likewise, the patient with the same symptoms who resides, for instance,

in Porto Rico, in which sprue is endemic, with only an occasional case of pellagra, would be diagnosed as having sprue.

William Murphy's<sup>109</sup> description of the gastrointestinal tract symptoms of pernicious anemia might apply as well to sprue or the subclinical type of pellagra. He describes them under the following:

1. Sore tongue or mouth, persistent
2. Diarrhea, intermittent
3. Anorexia
4. Nausea and vomiting
5. Altered gastric secretion—achlorhydria

Mental symptoms are frequent in pellagra, less frequent in sprue, and comparatively rare in pernicious anemia. Murphy, in discussing psychoses in pernicious anemia, said:

"Irrational states associated with marked psychosis are not uncommonly observed during acute relapse and at the time the blood levels are distinctly low. Improvement occurs concomitantly with the improvement of the physical state and an increased blood count."

**Diagnosis** — The question as to whether or not tropical sprue, nontropical sprue and idiopathic steatorrhea are identical disease entities of common origin seems nearer to solution. Snell,<sup>110</sup> in a report of 32 cases of tropical sprue, nontropical sprue and idiopathic steatorrhea, including a review of the recent literature on sprue, concluded that "distinctions among tropical sprue, nontropical sprue and idiopathic steatorrhea are largely artificial, the more intractable nature of the condition in the group of cases described under the last-mentioned caption being largely a matter of delayed diagnosis and inadequate treatment."

**Borderline Sprue**—Sprue is being diagnosed frequently all over the United States, not because of an increase in the number of cases, but for the reason that physicians have become sprue-conscious.

Physicians who are looking for sprue are observing many cases of red sore tongues (glossitis and stomatitis) and mild diarrheas, often associated with achlorhydria, which they are relieving by prescribing large doses of hydrochloric acid and by dietary management. Many of these cases are diagnosed as subclinical pellagra, and it may be added that in such cases it may be impossible to determine whether such cases are gastrogenic diarrhea, sprue or subclinical pellagra. Certain it is that in all 3 conditions the glossitis and diarrhea are cured by the use of a relatively low carbohydrate-high protein, rich vitamin diets.

**Treatment**—When the diagnosis of sprue, pellagra or pernicious anemia is made, the treatment found most effective in all of them is *liver*, or *liver extract*, and a high protein, relatively low carbohydrate, rich vitamin *diet*.

**Liver and Liver Extracts in Sprue**—Liver and liver extracts are known to be specific in the treatment of sprue; it is interesting to learn that Chinese joss "doctors" have been using liver for centuries in the treatment of conditions now known to be sprue. C. P. Rhoads<sup>111</sup> relates that Sir Patrick Manson began using liver in sprue in 1880. Manson had failed to cure a sprue patient, who was promptly cured by a Chinese joss "doctor" by the administration of pills of dried crow's liver. From that day Manson began curing his sprue cases with liver and mentioned it in his textbook in 1880.

There can be no doubt but that many clinicians have been using liver in some form in the treatment of sprue since the discovery of Minot and Murphy, in 1924, that the free use of liver will cure pernicious anemia. The same liver diet used in pernicious anemia will also cure pellagra and sprue.

The writer believes that whole fresh liver, or canned liver, is the best source of the sprue-preventive factor, because it is rich in all the other vitamins needed to prevent and cure sprue. Another reason why whole liver is preferred in sprue is that it is one of the best available sources of protein.

*Aqueous Extracts of Whole Liver*—Ruffin and Smith demonstrated that the aqueous extract of whole liver will cure pellagra in cases in which the extracts used parenterally have failed. The writer has used this preparation of whole liver with satisfactory results in sprue. It must be given in adequate doses, 3 ounces (90 cc.) a day for from a week to 10 days in attacks and after the symptoms subside  $\frac{1}{2}$  ounce (15 cc.) after each meal (3 times daily) should be continued for several weeks. Occasionally patients object to the taste of liver extract and prefer to take it in tomato juice, orange juice, or milk.

*Liver Extracts Parenterally*—The parenteral use of concentrated liver extracts is indicated when patients will not eat liver or refuse to take the aqueous extract of whole liver by mouth, or when there is nausea. Liver extract when given parenterally should be injected deep into the gluteal muscles. If the injections are painful, 1 or 2 cc. of 1 per cent solution of *novocain* may be added to the liver extract, or may be injected into the muscles with a small needle before the liver extract is given.

There are many liver concentrates manufactured by reliable pharmaceutical houses, but the writer has used Lilly's concentrated liver extract in 10 cc. ampoules more often than any other similar preparation. When used for macrocytic anemia, the dosage is  $3\frac{1}{8}$  cc., one-third of an ampoule, daily for 3 days, then twice a week; but when given during an attack of sprue in which liver in-

sufficiency seems pronounced, the contents of a 10-cc. ampoule should be given once or twice daily, until there is improvement in symptoms. In the severe cases of sprue, when death from acute liver insufficiency seems imminent, the use of large doses of liver extract may save the life of the patient.

*Sprue and Macrocytic Anemia Cured with Liver and Liver Extracts*—A dramatic cure of a severe case of tropical sprue with macrocytic anemia by the use of liver may be mentioned, because it illustrates the methods of using liver and liver extracts in such a case. For that reason the case will be reported in detail as follows:

The wife of an Army officer who had been stationed in the Philippines, aged 30, developed sore tongue, nausea, vomiting, mushy diarrhea, pronounced anemia, marked weakness, loss of flesh, nervousness and mental depression. She had been treated for amebic dysentery several times without improvement. She had grown worse in the past few weeks and her condition was considered serious when she was admitted to the Highland Avenue Baptist Hospital on May 4, 1938. Her height was 5 feet and she weighed 75 pounds at that time. She complained of a very sore mouth, nausea, vomiting, severe diarrhea, prostration and mental depression. She appeared anemic, and her skin had the lemon yellow tinge of pernicious anemia. Her hemoglobin was 45 per cent, red blood count 2,000,000, white blood count 7000, and smears for malaria were negative. Examination of gastric contents showed achylia. Repeated examination of warm specimens of feces were negative for *Endamoeba histolytica*. Her stools were large, foamy and mushy, containing much fat.

She was given a *blood transfusion*, and 1000 cc. of 10 per cent *dextrose in saline* intravenously every 8 hours, and no food was given by mouth for 24 hours; she also was given  $3\frac{1}{8}$  cc. of *liver extract*, in the gluteal muscles daily, for 3 days, then twice a week. When she was able to retain food, she was given 1 dram (4 cc.) of *dilute hydrochloric acid in milk* with meals and 3 hours after meals. Her food was increased

until she was taking about 4000 Calories of a moderately low carbohydrate-high protein *diet* with a banana and milk 3 hours after meals and orange juice every 2 or 3 hours if awake at night. She liked liver and was given fresh cooked liver for her noon meal (dinner) and canned liver for supper; and the liver extract parenterally was discontinued. She returned for a check-up in February, 1939. She reported that she had gained 29 pounds and had been in excellent health, her cheeks were rosy, and she presented the picture of a normal, attractive, vigorous woman. Her hemoglobin was 75 per cent, and the red blood count was 4,000,000. Examination of her stomach contents showed achylia. The *dilute hydrochloric acid* in a glass of *milk* with meals was continued. She had grown tired of liver, and liver extract parenterally twice a week was continued.

*Canned Liver in Nontropical Sprue—*

In 1930 the writer treated a sprue patient who also had pernicious anemia, in which dramatic improvement followed the use of canned liver.

*Case Report.*—A man, aged 50, height 5 feet 9½ inches, weight 107¾ pounds. He complained of "sore mouth, frequent stools, more in mornings and in evening after supper, weakness and loss of weight." Physical examination was negative except that his skin had the lemon tint characteristic of pernicious anemia. Physical examination was negative. Hemoglobin 55 per cent, red blood count 2,570,000, white blood count 7000. Wassermann, negative. Achlorhydria. No blood or parasites were found in several specimens of feces. He was a charity patient and could not buy liver extracts, and living in the country he could not get fresh liver regularly. He was advised to try canned liver. His neighbors also gave him the chicken livers when they ate chicken.

In addition, a *full diet*, eliminating corn bread and cane sugar products, was prescribed. His neighbors also gave him milk, to which he added 1½ drams (6 cc.) of dilute *hydrochloric acid* to each glassful, with meals and 3 hours after meals.

He returned for re-examination in 4 months, when his hemoglobin was 75 per cent, red blood count 4,250,000, and white blood count 7200. The glossitis and stomatitis had disappeared; the diarrhea had subsided and his

weight had increased to 160 pounds. He felt well and was working every day on a little farm. A year later his hemoglobin was 85 per cent, red blood count 4,600,000, and white blood count 8600.

Three and a half years later in 1937 he became careless about his diet and stopped eating the canned liver, when his sore mouth, diarrhea, weakness and anemia returned. At this time he had furuncles on the dorsal surfaces of his hands but the eruption bore no relation to the erythema of pellagra, and he gave no history of any pellagrous skin lesions. *His hemoglobin had dropped to 38 per cent; red blood count to 1,500,000, and white blood count to 5000.* He was advised to go back on canned liver and the dietary regimen he had followed in 1930. He has not been heard from since 1937.

In this case the use of dilute hydrochloric acid and an improved diet containing canned liver, a liberal amount of milk and eliminating corn bread, syrup and other cane sugar products, relieved the stomatitis and diarrhea of sprue and brought the hemoglobin and red blood count to normal. Recrudescence of the symptoms of sprue followed when he left off the canned liver and returned to his former dietary habits, when the hemoglobin dropped to 38 per cent, red blood count to 1,500,000. This patient lives some distance from Birmingham and he has not been seen or heard from since his last visit when his low blood count proved the correctness of the diagnosis of pernicious anemia.

There were no other cases of sprue in the locality in which this patient lived. Likewise, the patient had not heard of any cases of pellagra in his neighborhood. The cause of the disease could not be determined, although it is probable that he was undernourished before he had symptoms of sprue. It, therefore, seems justifiable to diagnose this case as nontropical sprue.

If this case had been in Boston, it probably would have been diagnosed as

pernicious anemia; and if it had occurred where there were cases of pellagra, it probably would have been called subclinical pellagra. Certain it is that the treatment given him would have cured sprue, pellagra or pernicious anemia.

Since such happy results followed the use of canned liver in this case, a number of sprue and pellagra patients who could not buy fresh whole liver or liver ex-

tracts have been benefited or cured by the use of this cheap canned liver. It is admitted that the results of using canned liver have not been studied in a large series of cases in either sprue or pellagra but the clinical results in a number of cases have been so favorable that canned liver is advised as the one most important article of diet in sprue and pellagra where fresh liver is not available.

## DIETOTHERAPY

By DEACONESS MAUDE BEHRMAN, B.S.

### Diabetes Mellitus

The present treatment of diabetes mellitus is reviewed by Sansum.<sup>112</sup> After giving a brief history of diabetes and the various forms of treatment, he states that more than 50 per cent of all diabetic patients need only the proper diets and that many need only take insulin when starting treatment.

The type of diet which is most commonly used today is not very different from the normal adequate diet. The 3 ways in which it differs are that (1) no concentrated sweets are used; (2) definite proportions of food are given at regular intervals; and (3) the food is weighed or accurately measured. If the amount of food taken at each meal is the same, the diabetic is able to utilize it much better, even though he does not receive insulin. In his diets, he recommends equal amounts of carbohydrate in the 3 meals, but does not believe it necessary to do so with the protein and fat. Feedings in between are recommended for diabetic children. When modified insulin is used, then the food distribution may be different, since the amount of food absorbed must parallel the amount of insulin liberated. Sansum suggests that slightly less carbohydrate be given at breakfast and more at the noon and

evening meal. A smaller amount of protein is also given at breakfast than in the other meals. The fat is rather evenly distributed. Equal amounts of carbohydrate must be given in small meal in between regular meals and also at bedtime. Some protein and fat should be included in the bedtime feeding, since this is more slowly utilized and helps to offset the reactions formerly received from insulin during the night. Table IV shows the way he suggests that the carbohydrate, protein and fat be distributed *i. e.*, with the use of modified insulin.

Good results are obtained by using insulin and as simple a dietary regimen as is possible, which also means that the diet is weighed for a while. Later on the patient learns to visualize the size of portions (*from weighing the food*) and may estimate the amounts with quite a good deal of accuracy. If any question about the patient's condition arises, the diet should be weighed again. A patient with a severe diabetic condition should always weigh his food, according to this author.

The patient should be put on a maintenance diet which will meet his need as quickly as possible. When optimal nutritional requirements are met, the diabetic usually improves.

TABLE IV

	Normal Meal	A M	Noon Meal	P M	Evening Meal	Bed-time
Carbohydrate	25	5	30	5	30	5
Protein	20		30		40	10
Fat	30		30		30	10

The diet of the average diabetic adult needs to be changed but seldom. If complications arise it may be necessary to change the figures. A diabetic child's diet should be changed at least once a year and more often during certain ages. In this manner the demands of growth and development will be met.

If severe *ketosis* develops, the first step in the treatment is to give **carbohydrate** as an adjunct to **insulin**. This carbohydrate should be in a form which is quickly available to the body, such as **glucose, fruit juices, skimmed milk** or **sweetened beverages**. When ketosis disappears, the diet is built up as quickly as possible to the maintenance requirements.

The *overweight diabetic* is treated for obesity. He should be given a diet consisting of from 1000 to 1500 Calories. This low calorie diet will also control the diabetes. The carbohydrate should be in the ratio of 4 parts to 1 part of fat and an extra amount of protein. The findings of Joslin showed that 77 per cent of his patients were overweight at the onset of diabetes. Since overeating is the most common cause of overweight, most middleaged patients can be treated with diet alone. Newburgh and Conn<sup>113</sup> found that their obese patients had normal oral and intravenous glucose tolerance curves when they were reduced to normal weight.

If the diabetic is *underweight* from loss of sugar, he should be given a **high**

**caloric diet** with the same ratio of carbohydrate to fat as that used in the maintenance diet. The amount of protein is normal. As soon as the weight is ideal, the caloric value of the diet is reduced.

The *diabetic with peptic ulcer, colitis* or *allergy* may require a **modified diet** until the condition clears up.

Sansum believes that because carbohydrate in these diets increases insulin production, thereby improving the liver function because of decreased fat deposition and increased glycogen storage, the patients are more energetic, more alert mentally, and the diabetes improves. The protein ranges from 60 to 100 grams. Too much protein stimulates the metabolism. The fat ranges from 75 to 150 grams. The safe ratio, he explains, is 1 part of fat to 2 parts of carbohydrate for the adult and 1 part of fat to 3 to 4 parts of carbohydrate for children. Vascular complications seem to be decreased with the lower fat content of diet. Consideration of fats low in cholesterol may help in the prevention of blood-vessel degeneration. Mineral and vitamin requirements should be the same as normal. The diabetic diet with large amounts of fruits, vegetables and whole grains, supplies plenty of minerals and vitamins. This may be advantageous in view of the relationship between vitamins and hormones and of both to carbohydrate metabolism.

The diabetic should have enough **fluid intake** to produce at least 2000 cc. of urine daily. This may prevent mistakes in the testing of urine which is too concentrated. The fluids may be in the form of water, fruit juices and milk. The loss of sugar, water and salt in the uncontrolled diabetic raises the amount of fluid intake. The thirst which he experiences usually leads to the use of plenty of fluid.

Since fruits, vegetables and whole grains are high in fiber content, it is possible to prevent constipation, since these foods are abundant in the well planned diabetic diet.

The 2 most recent changes found in diabetic diets are:

(1) Lowered cholesterol content.

(2) Increased vitamin content, particularly that of the vitamin B complex.

The smallest amount of *insulin* which Sansum gives is between 15 to 20 units, daily. In severe cases he may give as much as 100 to 150 units. The normal pancreas may possibly secrete 100 units of insulin in 24 hours. It possibly has the ability to secrete from 3 to 4 times that amount in an emergency.

Up to the present much attention has been given to the glucose value of the foods. Sansum believes that since insulin is concerned in the metabolism of fat and protein as well as glucose, the capacity of insulin to utilize various foods becomes more important than its capacity to metabolize the glucose formers alone. The diet should be considered as a whole when adjusting the insulin. Approximately 1 unit of insulin is required for the addition of each 2 grams of food, or approximately 10 units for the addition of each 100 Calories. Urine and blood sugar findings finally determine the amount which may vary with various metabolic disturbances.

The use of modified insulin has also made it necessary to give the frequent feedings because of the slow liberation of the insulin. Other factors such as exercise, rest, elimination of focal or systemic infection, correction of digestive disturbances and faulty elimination must all be considered when planning the diabetic diet. Diarrhea in the diabetic is serious and should not be neglected. It may lead to dehydration, acidosis, and

the failure of the body to absorb food, especially the carbohydrate. It may be necessary to increase the fluid and carbohydrate.

### Vitamin Requirements

In a paper presented before the recent American Dietetic Association Convention, Sherman, of Columbia, discussed the vitamins measured in the language of the units which will give the body vigor. He said that body vigor increased when the intake was as much as 4 times that necessary to keep the individual in normal health. He believes there is evidence that a generous supply of these foods which give vitamin C, such as citrus fruits, and succulent and leafy vegetables, might have a part in warding off the characteristics of old age.

Carroll Palmer, of the United States Public Health Service, explained that the vitamin requirement of individuals differs considerably. Some need a great deal more than others. He also explained that those who are too conscious of their own diet and who can remember what they have had to eat, are usually victims of fads or trick diets. These individuals are often lacking one or more of the essential food elements.

Hazel Munsell, United States Department of Agriculture, states that foods are never the same in composition. One orange in a dozen will have twice the amount of vitamin C as another. Spinach varies depending on the length of time it lays in the market. A tomato rained on has less food value than one on which the sun has been shining. Tables of food values are a check, for use in determining which foods are poor sources, good sources, or excellent sources of the constituents. The persistent use of a wide variety of foods was stressed, *i. e.*, ALL meats, ALL fruits, ALL vegetables, natural whole grains, brown rice and



plenty of the protective foods, such as milk, leafy vegetables, eggs and butter.

### Mineral Waters

In discussing the relationship of naturally carbonated mineral water to general nutrition and dietary deficiencies, McClellan<sup>114</sup> considered the value of certain kinds of *mineral waters* to nutrition and the importance of these minerals to the body. The subject is included in this section because it may be of value to physicians who are prescribing diets inadequate in minerals. Analyses of the water from 6 springs found at the Saratoga Spa, New York, are given in table form.

The importance of minerals is well known, and the frequency of deficiencies of calcium, phosphorus, and iodine need not be discussed. Sulphur is seldom deficient in diets, since it is found in the amino-acids of proteins containing cystine. Magnesium and potassium are seldom deficient, also sodium and chlorine are usually abundant, generally from 10 to 12 grams being a common daily intake. Other minerals such as copper, manganese, fluorine, silicon and aluminum are needed by the body.

Often it is necessary to supplement the diet with minerals. It is a well known fact that soil in which foods are grown often becomes depleted and naturally the foods grown will have a lowered mineral content. One quart of Hathorn or Coesa Water will provide the daily requirement of calcium and phosphorus. The iodine requirement may be provided by from  $\frac{1}{2}$  to 1 ounce. There are also small amounts of potassium and iron which need not be overlooked. Phosphorus and sulphur are

missing, but it is significant that these are better when taken in organic form. The *child who cannot drink milk* may receive some of his *calcium* requirement *in water*. During *pregnancy and vomiting* it may be necessary to increase the mineral intake. The *carbon dioxide* often relieves the irritated stomach when no other food may be taken.

McClellan lists other diseases in which he believes the water may be of value and gives the reasons as follows:

*Addison's Disease*—The high sodium content is of value since in Addison's disease the sodium chloride should be increased.

*Rickets*—Tetany develops when the calcium of the blood drops below 7-8 mg. per 100 cc.

*Allergic Diseases*—High calcium diets are now being used in place of elimination diets.

*Colitis*—Often a low blood calcium is found as a symptom in this disease.

*Febrile Conditions*—Mineral water may help to maintain the alkaline reserve at normal level, thereby preventing the high acid urine.

*Gout and Uric Acid Diathesis*—Uric acid is more soluble in an alkaline medium.

*Nutritional or Hypochromic Anemia*—The iron found in the mineral water is in the ferrous form, which is more easily utilized by the body.

*Thyroid Disorders*—In disorders of the thyroid, the iodine may have the wrong effect, producing symptoms which may mean the water must be checked.

*Renal Insufficiency*—The loss of basic minerals, leading to a severe acidosis because of increase in the fixed acid radical, such as sulfate and phosphate, may occur. Alkaline bases such as sodium, potassium, calcium and magnesium, must be supplied.

*Renal Calculi*—When the stones are those deposited in acid media, such as oxalates and urates, the urine should be changed to the alkaline side.

In conclusion, McClellan states that the use of mineral water should be controlled by a physician.

## VITAMINS

By JOHN H. WILLARD, A.B., M.D.

**Introduction**—In the ever widening field of vitamin knowledge, some interesting suggestions have been made recently regarding a possible *relationship between hormones and vitamins*. As yet adequate information for final judgment is lacking but suggestive evidence has been published. Eller and Wolff<sup>115</sup> state that "close physiologic interrelationship is said to exist between certain hormones and vitamins." Murlin is quoted as stating that "vitamins might properly be regarded as exogenous hormones or hormones may be regarded as endogenous vitamins."

Experimental work has shown an antagonistic relation between vitamin A and thyroxin. *Thyrotoxicosis* in animals may be prevented or cured by the use of vitamin A. Conversely, hypervitaminosis A in animals can be prevented and cured by thyroid medication. In guinea-pigs vitamin A has been found to inactivate the thyrotropic pituitary hormone. Beneficial effects of vitamin A in human thyrotoxicosis were reported by Wendt as early as 1935.

A possible interrelation between the *B complex* and the *anterior pituitary* is suggested by work reported by Sutton and Ashworth.<sup>116</sup> Four of 5 pellagrins, who were amply treated with nicotinic acid and B complex without improvement, were definitely benefited by anterior pituitary medication. In 2 instances glossitis and diarrhea disappeared.

Vitamin D is closely related chemically to the sterols found in *sex hormones*. According to Murlin,<sup>117</sup> "cholesterol may be converted into the male sex hormone; the male sex hormone is readily convertible to estrone and this, in turn, to progesterone. Testosterone is

very similar structurally to ergosterol and vitamin D."

*Parathyroid* function is also closely related to vitamin D in the control of the calcium and phosphorus metabolism. Both parathyroid extract and vitamin D, if given in large doses, produce an increase in blood calcium levels. Animals with parathyroids removed can be kept from hypocalcemia tetany by the administration of vitamin D.

*Vitamin C* seems closely related to the functions of several glands, of which the *pituitary, corpus luteum* and the *adrenals* seem the most important. Analysis has shown a considerable content in these glands of ascorbic acid or a closely related substance.

**Symptoms and Signs of Deficiency**—Mackie, Eddy, and Mills<sup>118</sup> have summarized the symptoms and signs of deficiency of the various vitamins in Table V.

## Vitamin A

The importance of vitamin A to the normal health of epithelial tissues and to normal retinal activity has been well established. Keratinization of epithelial tissues and night blindness are the most common evidences of an inadequate supply of this vitamin. Deficiency may result from insufficient intake, faulty absorption, as in jaundice or intestinal disease, and from faulty storage in liver disease.

The requirements of the body for vitamin A have been variously estimated at from 3000-6000 international units for adults and 6000-8000 for growing children.

**Incidence of Deficiency**—Lehman and Rapaport<sup>119</sup> quote the U. S. Department of Agriculture as finding that two-thirds of the present-day diets, even

TABLE V  
SYMPTOMS AND SIGNS OF VITAMIN DEFICIENCY  
(Mackie, Eddy and Mills· *Ann Int. Med* )

Vitamin	Symptoms	Signs
A	Night blindness	{ Dry scaly skin Follicular hyperkeratosis Bitots spots
Thiamin B <sub>1</sub>	{ Anorexia Peripheral neuritis Cardiac failure	{ Muscle tenderness Hyperreflexia—areflexia Diminished vibratory sense Tachycardia
Riboflavin	?	{ Cheilosis Seborrheic dermatitis Glossitis Keratitis
Nicotinic acid	{ Painful mouth and tongue Diarrhea, dermatitis Psychosis, stupor	{ Inflamed, denuded tongue Dermatitis, symmetrical, scrotal, vulval, perianal
B <sub>6</sub>	Weakness, insomnia, nervousness (?)	?
Ascorbic acid C	{ Bleeding Pain	{ Petechiae Spontaneous hemorrhage
D	{ Rickets Weakness	{ Cessation of bone growth Disturbed Ca-P metabolism Osteoporosis
E	Habitual abortion ?	Muscular dystrophy ?
K	Bleeding	{ Petechiae Spontaneous hemorrhage

when expenditures for food are relatively high, contain insufficient vitamin A to insure good visual adaptation in semi-darkness.

An interesting side-light on the frequency of deficient diets is an analysis of hospital ward and clinic patients by Scott and Janeway.<sup>120</sup> It was found that 46 per cent were deficient in vitamin A intake. Average ward diets were found to contain adequate nutritional substances to prevent deficiency states but were not adequate to treat deficiencies.

**Diagnosis**—There is still considerable disagreement concerning the value of biophotometric determinations as an index of vitamin A deficiency. Steininger, Roberts, and Brenner<sup>121</sup> studied blood levels of carotenoids (precursors

of vitamin A) and vitamin A by colorimetric methods and compared these findings with biophotometric readings. No correlation was found. These workers suggest that although there is some relation between biophotometric readings and the nutritional status of the subject, this relationship is not close enough to use as a clinical procedure. Further experimental studies with the blood technic included placing the subjects on a diet low in vitamin A for a period of 4 months. It was found that:

“(1) The original level of vitamin A in the blood of the subjects was related to their dietary histories.

“(2) The blood values of vitamin A fell rapidly when the subjects were placed on a vitamin A low diet, although

there was considerable variation noted between individual determinations.

"(3) Small supplements of vitamin A caused the amount of this substance in the blood to rise rapidly but had no effect on the carotene.

"(4) The vitamin A blood level reached after a supplement and the length of time that this level was maintained were both affected by the size of the supplement given.

"(5) The average amount of vitamin A in the fasting blood of subjects receiving a supplement of vitamin A was significantly higher than that of subjects who had no supplement."

**Treatment**—The best food sources are *milk, butter, egg yolk, liver, carrots, green leafy vegetables*. Pharmaceuticals include *fish liver oils* (cod, halibut) and *carotene*. For therapeutic purposes 30,000-100,000 international units may be given daily. Eller and Wolff<sup>1</sup> state that as yet symptoms of overdosage have not been observed.

### Vitamin B Complex

Out of the large mass of literature dealing with specific effects of the components of the B complex, one fact is becoming clearer, *i. e.*, single deficiencies are clinical rarities. Even beriberi and pellagra, which are primarily due to lack of adequate B<sub>1</sub> and nicotinic acid, respectively, usually are complicated by degrees of deficiency of other factors of the complex and by deficiency of other vitamins. A close interrelation between components of the B complex has been noted. Therapy with sources of the entire complex is advised in any deficiency state, with added specific factors as they may be indicated.

**Sources**—Natural sources include whole grains, egg yolk, liver, leafy vegetables and yeast. Concentrates prepared from yeast or liver are available. Recent

data indicate that liver extracts are questionable sources of the various factors of the B complex, since purification and concentration result in considerable loss of these materials. Williams and Spies<sup>122</sup> state that liver contains about 3 mg. of B<sub>1</sub> per kilogram. For normal requirements an extract from 0.5 to 1 kg. of liver would be necessary. This would require from 3 to 10 cc of very concentrated liver extract daily if none of the B<sub>1</sub> content were lost in concentration, an obviously uneconomical method of supplying this factor.

The B<sub>2</sub> content of liver is similar. Stepp, Kühnau and Schroeder report the riboflavin content of liver to be 15-17 mg. per kilogram. Average requirements would necessitate the daily administration of extract from 100 to 200 Gm. of liver.

The importance of the entire complex in human deficiencies is illustrated by the experimental case reported by Elsom, Lukens, Montgomery, and Jonas<sup>123</sup> Among the changes noted were edema, a tendency toward decreased glucose tolerance, increase in blood lactic acid and decreased response to insulin. Thiamin produced some improvement, as did thiamin and riboflavin but complete recovery did not occur until brewer's yeast was added (1¼ ounces—42 Gm. daily).

To understand the various pictures seen in deficiency states and to appreciate the possible therapeutic value of the newer synthetics, however, it seems wise to discuss the separate factors as far as present information permits. Component parts of the B complex are numerous. Those of known importance to human nutrition include: Vitamin B<sub>1</sub> (thiamin); B<sub>2</sub> or G (riboflavin); P-P factor (nicotinic acid); B<sub>6</sub> (pyridoxin); and possibly pantothenic acid (filtrate factor?) and yeast adenylic acid (Spies).<sup>124</sup>

### Vitamin B<sub>1</sub> (Thiamin)

The clinical picture of advanced B<sub>1</sub> deficiency is believed to be beriberi, which is characterized by peripheral neuropathy with degeneration of associated muscles, edema, cardiac dilatation with rapid pulse and high pulse pressure. Early symptoms include loss of weight and appetite, dizziness, burning sensations, numbness, tenderness and cramps

and damage. The *cardiovascular symptoms* are probably largely dependent upon changes in the autonomic nervous system but are also associated with myocardial degeneration. *Digestive symptoms*, usually anorexia, diarrhea and glossitis, are probably largely the result of secretory disturbances secondary to nerve changes but may also depend on atrophy of secretory cells.

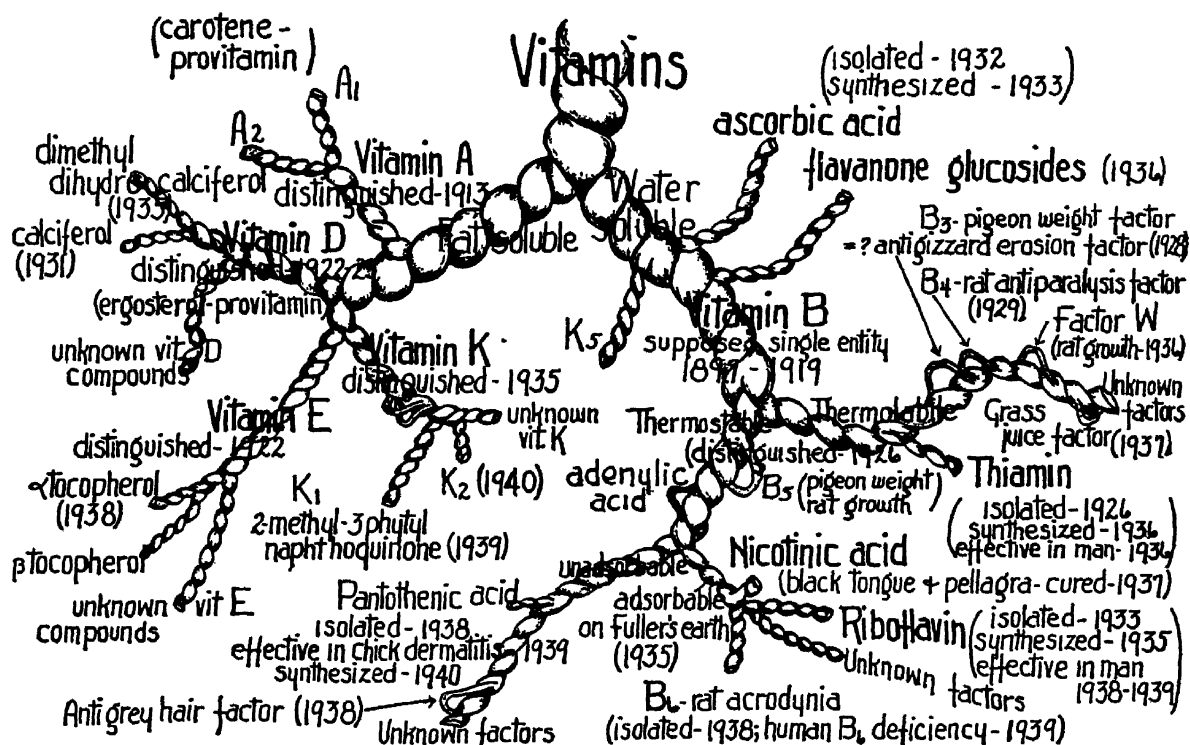


Fig. 3—Diagrammatic representation of interrelationship of vitamins. They are schematically differentiated into water-soluble and fat-soluble fractions, the latter group is further separated into its thermolabile and thermostable components. Certain of these substances have been shown to be essential to human nutrition and effective in treatment of specific deficiency diseases. The physiologic properties of many are as yet undetermined. (Spies, Hightower and Hubbard: J. A. M. A.)

of muscles (usually calf). Thiamin relieves these symptoms if they are due to B<sub>1</sub> deficiency.

**Physiology and Pathology**—Experimental work has shown B<sub>1</sub> to be closely related to intracellular metabolic activity. All tissues may be affected but primary effects are degenerative changes in *nervous tissue*. If this process is arrested in time, regeneration occurs, but extensive degeneration results in perma-

**Experimental Deficiency**—Jolliffe and coworkers<sup>125</sup> experimented on normal individuals with diets furnishing 43 to 63 per cent of adequate B<sub>1</sub> as calculated by the Cowgill formula (10 units per 100 calories of food intake). Subjective symptoms of deficiency appeared in from 4 to 13 days and objective evidence of deficiency, as shown by electrocardiographic changes and hyperesthesia of calves and feet, appeared in many. Uri-

nary excretion of B<sub>1</sub> fell below 30 per cent of the control level. All symptoms disappeared after 3 to 6 days of adequate B<sub>1</sub> intake.

Williams, Mason, Wilder, and Smith<sup>126</sup> placed 4 healthy females on a diet containing less than 50 units of B<sub>1</sub> daily but adequate otherwise for a period of 88 days. Two additional patients were placed upon the same program, but after 11 days received gradually increasing doses of thiamin without their knowledge. The 4 patients with deficient intake all developed striking evidences of deficiency. Similar signs appeared in the 2 controls until the thiamin intake reached 0.95 mg. per day. Further increase of intake to 2 mg. per day produced definite improvement in ability to work and in alertness.

The chief symptoms of B<sub>1</sub> deficiency in these patients were fatigue, lassitude, anorexia followed by actual intolerance to food with uncontrollable vomiting. This picture simulated closely that usually called *neurasthenia* with *anorexia nervosa* developing later. Studies also showed delayed gastrointestinal motility and altered T-waves by electrocardiography during deficiency which returned to normal with adequate thiamin intake. The rapidity with which the signs of deficiency occurred depended upon the amount of physical activity, and apparently also bore a relationship to the season of the year, symptoms occurring more quickly during the winter months.

Of particular interest was the absence of the usual picture of beriberi. No edema, cardiac dilatation or neuritis was seen in these patients. A slight tenderness of the calves with paresthesia of feet and legs, however, did occur. The authors question whether B<sub>1</sub> lack alone is responsible for the clinical picture of beriberi.

**Diagnosis**—As yet no simple clinical method has been developed to determine B<sub>1</sub> deficiency. Experimentally, several methods of measuring *urinary excretion* have been applied with some success. Borson<sup>127</sup> reports experience with a colorimetric method based on the conversion of urinary thiamin into thiochrome by the use of ferricyanide. It was found that persons on an adequate diet excreted from 100 to 300 micrograms per day. If a test dose of thiamin of 0.1 mg. per kilogram of body weight is given by mouth, 8 to 10 per cent is excreted. By using such test doses, the degree of deficiency may be determined by the number of doses necessary to produce normal secretion. In deficient patients it was found that up to 100 mg. might be necessary to produce saturation.

The author reports studies on patients with various disorders. There is evidence that *diarrhea* may often lead to deficiency. *Diureses* may contribute to deficient states by washing out additional thiamin which is apparently a renal non-threshold substance. *Liver disease* increases excretion probably because of inability of phosphorylation necessary for normal utilization and storage. *Thyrototoxicosis* was frequently associated with deficient excretion. Patients with *multiple sclerosis* and *central nervous system lues* were frequently deficient and many responded favorably to adequate intake. Improvement also occurred in several cases of *tic douloureux* who were shown to be deficient by this method.

Robinson, Melnick, and Field<sup>128</sup> state that "under proper conditions, the level of the urinary excretion of thiamin permits an objective determination of the state of thiamin nutrition in the human subject." In normal subjects on an adequate diet the 24-hour excretion averaged 90 micrograms for males and 60

micrograms for females. In those with subnormal diets the excretion was 66 micrograms or less in males and 43 or less in females. A test dose of 5 mg. of thiamin resulted in excretion of 7.5 per cent in normals but below 7 per cent in those on deficient diets. The same workers<sup>129</sup> found that urinary excretion did not bear a constant relation to the bisulphite binding substances in the blood, a previously suggested measure of B<sub>1</sub> saturation.

**Treatment**—For mild deficiencies without marked gastrointestinal symptoms, food sources are preferable. These include *whole grains, egg yolk, liver, green vegetables* and *yeast*. Concentrated sources include *liver* and *yeast extracts*.

It is generally accepted that  $\frac{1}{65}$  grain (1 mg.) of *thiamin* daily (333 units) offers an adequate maintenance supply under normal conditions. In beriberi, Spies, Hightower, and Hubbard<sup>124</sup> recommend  $\frac{1}{3}$  grain (20 mg.) daily in  $\frac{1}{6}$  grain (10 mg.) doses for mild cases and  $1\frac{2}{3}$  to  $3\frac{1}{3}$  ounces (50 to 100 mg.) in severe cases. During the acute phase, 1 ounce (30 Gm.) of dried *brewer's yeast* 3 times daily is suggested as a supplement to the normal diet. Improvement is usually prompt but prolonged administration may be necessary in some cases with extensive nerve changes.

### Vitamin B<sub>2</sub> (G or Riboflavin)

Recent advances have shown that what was originally termed vitamin B<sub>2</sub> is in reality composed of many factors, including riboflavin, B<sub>3</sub>, B<sub>4</sub>, B<sub>5</sub>, B<sub>6</sub> and nicotinic acid. Under present terminology B<sub>2</sub> is synonymous with riboflavin.

**Deficiency**—Riboflavin is similar to nicotinic acid in its relation to intracellular metabolic activity. Evidence of ariboflavinosis is usually associated with signs of pellagra. Deficiency is indicated

by the presence of cheilosis (fissuring lesions at the corners of the mouth) and lesions around the eyes and a shark-skin appearance over the nose (Spies). Itching, burning, excessive dryness of the eyes, photophobia, redness of the conjunctiva are eye symptoms of this deficiency.<sup>130</sup> Keratitis also has been described.<sup>131</sup> Workers call attention to the relatively high incidence of ariboflavinosis as an apparently uncomplicated avitaminosis.<sup>132</sup>

**Treatment**—Dietary sources include *milk* and *milk products, eggs, green vegetables, yeast, liver, wheat germ* and *kale*. Oral administration of 3 to 5 mg. of synthetic *riboflavin* is suggested for treatment of definite deficiency. Dried *brewer's yeast*,  $1\frac{2}{3}$  to  $2\frac{1}{2}$  ounces (50 to 75 Gm.) daily also furnishes adequate riboflavin for therapy (Spies).

### Nicotinic Acid

There is adequate proof that nicotinic acid and its related compounds (nicotinic acid amide, sodium nicotinate, and nikethamide) will relieve most of the symptoms of pellagra. Spies<sup>124</sup> summarizes the *oral* symptoms of pellagra as consisting of glossitis, stomatitis, gingivitis, and pharyngitis. *Digestive symptoms* include nausea, vomiting, ptyalism, diarrhea and abdominal distention. The *dermal lesions* may occur in any part of the body but are usually symmetrical and are sharply demarcated. At the onset the lesions may suggest sunburn, later followed by desquamation, leaving thickened, pigmented skin. *Mental* disturbances may include apprehension, confusion, disorientation, hallucinations, mania and delirium.

The earliest symptoms are not diagnostic but should suggest early deficiency, according to Spies.<sup>124</sup> These include loss of weight and strength, lassi-

tude, abdominal pain, numbness, nervousness and forgetfulness. A syndrome consisting of hyperesthesia, increased psychomotor drive, anxiety and apprehension, with a tendency toward depression, weariness and increased fatigability, headaches and sleeplessness, is typical of this prodromal period.

**Diagnosis** — No laboratory procedures have proved satisfactory for demonstrating deficiency of nicotinic acid, the diagnosis depending upon the clinical picture previously described.

**Treatment**—Prompt relief of the above symptoms is produced by administration of adequate nicotinic acid or related compounds, although, as noted previously, other components of the B complex may be necessary for complete cure. Spies and his coworkers have suggested the use of 5 to 8 grains (300 to 500 mg.) of *nicotinic acid* daily divided into  $\frac{3}{4}$  grain (50 mg.) oral doses. Two-thirds to  $1\frac{1}{3}$  grains (40 to 80 mg.) may be given daily in normal salt solution intravenously. Improvement should be noted in 24 to 72 hours by either method.

### Vitamin B<sub>6</sub> (Pyridoxin)

Although the presence of this factor in the B complex was postulated in 1935 by P. György, who gave the name B<sub>6</sub> to the rat-pellagra-preventive factor, it was not until 1938 that its importance in human nutrition was proved. In 1939, Spies and coworkers<sup>133</sup> reported the favorable response to administration of synthetic B<sub>6</sub> in patients with deficiency diseases who had not recovered completely on supplements of thiamin, riboflavin and nicotinic acid. These workers described the symptoms as including nervousness, insomnia, irritability, cramping pains in the stomach, weakness, muscular rigidity and difficulty and awkwardness in walking.

A further report was made by Spies, Ladisch, and Bean<sup>134</sup> on 20 additional patients. By using a method of determining urinary excretion, a saturation test was conducted on patients as well as controls. It was found that after the intravenous injection of 50 mg. of pyridoxin (B<sub>6</sub>), the deficient patients excreted only small amounts in the urine during the next hour (0 to 0.4 per cent) while normals excreted from 5.4 to 13.2 per cent of the test dose in 1 hour.

Because of the observed benefits on muscular weakness and rigidity, B<sub>6</sub> has been used in Parkinson's syndrome<sup>124, 135</sup> and in pseudohypertrophic muscular dystrophy.<sup>136</sup>

**Dosage**—No standard therapeutic program has been evolved. Antopol and Schotland<sup>136</sup> used doses from  $\frac{3}{4}$  to  $2\frac{1}{4}$  grains (50 to 150 mg.) subcutaneously each week in single or divided doses. Spies, Ladisch and Bean<sup>134</sup> reported spectacular results from single  $\frac{3}{4}$ -grain (50-mg.) doses.

### Yeast Adenylic Acid

Spies and his coworkers<sup>124</sup> found that in some patients with *malnutrition* but without definite evidence of pellagra, severe burning of the mouth and tongue was relieved by the administration of *adenylic acid*. It also seemed to enhance the effect of nicotinic acid in *pellagrins*. Doses up to 3 grains (200 mg.) may be given by mouth.

### Pantothenic Acid

This member of the B complex has been called the chick antidermatitis factor. Spies and his coworkers<sup>124</sup> found that, in humans with deficiency diseases, the blood levels for this substance were decreased. No conclusive evidence of the importance of this factor in human nutrition, however, is at hand at present.



### Vitamin C (Ascorbic Acid)

**Diagnosis of Deficiency**—The relation of vitamin C deficiency to scurvy has been amply demonstrated. It has been shown that the hemorrhagic tendencies in scurvy are dependent upon increased capillary fragility resulting from imperfect intercellular cement substance in the endothelial linings. The degree of deficiency necessary for the appearance of scorbutic symptoms has been widely studied with variable results. *Blood levels* above 1 mg. per 100 cc. are considered normal. Levels below 0.5 mg. per cent indicate deficiency and potential scurvy. Many persons with low levels, however, do not show scorbutic symptoms.

The degree of deficiency has been further studied by estimating body *saturation*. This has been done by giving test doses and estimating percentage excretion in the next few hours. Ordinary urinary excretion without test doses is not a reliable index. Some workers have advised large doses for several days before trying a tolerance test to determine the total amount necessary to produce saturation. Bauman states that after  $\frac{3}{4}$  to  $1\frac{1}{2}$  grains (50 to 100 mg.) of ascorbic acid for 3 or 4 days, the urinary excretion should amount to 60 to 80 per cent of the test dose in normal persons.

*Capillary fragility* has been studied as a possible index of vitamin C saturation but it has proved unreliable.

Crandon, Lund, and Dill<sup>137</sup> studied *experimental deficiency* by feeding a diet completely lacking in vitamin C to a normal adult for a period of 6 months. The plasma ascorbic acid fell to a low level within 10 days and disappeared in 30 days. The first clinical sign of deficiency appeared after 132 days (13 weeks after the blood level reached zero). It was found that the vitamin C content of the

white cell-platelet layer of centrifuged blood was a more accurate indication of impending scurvy than determinations in plasma. The earliest clinical signs were hyperkeratotic papules. Perifollicular hemorrhages did not occur until after 161 days on the deficient diet. The early signs suggested vitamin A deficiency. Weakness occurred after 3 months and progressed. *Wound healing* was delayed at the time of the first symptoms (141 days). Intravenous injection produced rapid disappearance of symptoms and signs. The blood level of ascorbic acid became normal after 4 daily injections of 15 grains (1 Gm.) of ascorbic acid. Urine studies at this time, however, did not indicate complete saturation.

The authors calculate the *daily requirement* as being between  $\frac{1}{2}$  and  $\frac{3}{4}$  grains (30 and 45 mg.) per day (600 to 900 units). The relative *incidence* of subnormal vitamin C intake is indicated by figures quoted by Fincke.<sup>138</sup> Urinary excretion was tested in female college students in various parts of the country. It was found that in the northwest 30 to 35 per cent of the students showed subnormal excretion (below 20 mg. in 24 hours). In Massachusetts and Rhode Island the figure rose to 70 to 80 per cent.

Bartlet, Jones and Ryan<sup>139</sup> determined plasma ascorbic acid on 188 hospital patients. Two-thirds were below 0.5 mg. per 100 cc., or in the potential scurvy level. Operation consistently reduced the preoperative level, with a gradual return to preoperative levels or above. Studies of urinary excretion showed that the decreased blood content was not due to increased urinary loss. Saturation tests after operation suggested an increased demand for vitamin C, possibly due to increased utilization for tissue repair.

**Relation to Heavy Metals**—Holmes, Campbell, and Amberg<sup>140</sup> reported prompt relief of symptoms in painters with lead poisoning following the administration of ascorbic acid. Subsequent work, however, tends to discredit the value of vitamin C for treatment purposes. Pillimer, Seifter, Kuehn and Ecker<sup>141</sup> studied the effect of lead on vitamin C metabolism in guinea-pigs. It was found that animals on a low ascorbic acid intake given lead carbonate developed more severe lead poisoning than those on an adequate vitamin C intake and that the neurologic signs of plumbism were absent in the latter. No change in vitamin C metabolism was noted, however, discrediting the theory of Holmes and his associates that ascorbic acid combined with lead, producing an inactive compound.

Farmer, Abt and Aron<sup>142</sup> studied the possible relation between arsenic, bismuth and iron and ascorbic acid. Luetics who tolerated *arsenicals* poorly were found to require very large doses of ascorbic acid to elevate the plasma level to normal. *Bismuth* had little influence on plasma vitamin C levels, while *iron* produced a marked decrease in plasma vitamin C.

No relationship between vitamin C saturation and toxic symptoms from arsenic was found by Falconer, Epstein and Mills,<sup>143</sup> who studied 6 patients with *thrombocytopenic purpura* produced by arsphenamine or bismarsen.

### Vitamin D

It has been established that many sterols, upon activation by exposure to ultraviolet light, exhibit the properties of vitamin D.<sup>144</sup> The most widely used preparation is irradiated ergosterol, also known as calciferol or vitamin D<sub>2</sub>. The normally occurring vitamin D in fish oil has been labelled D<sub>3</sub> and is probably the

same as that produced by ultraviolet on the skin.

Vitamin D is intimately related to the metabolism of calcium and phosphorus. Park<sup>145</sup> states that the exact mechanism is unknown. Absorption of calcium and phosphorus from the gastrointestinal tract is increased by vitamin D. The metabolism of calcium and phosphorus is closely related to parathyroid function and hence vitamin D is in some way linked to the function of this gland, although the exact relationship is unknown as yet.

Clinically, the chief interest in vitamin D is in relation to the treatment of *rickets*. Recent articles dealing with the value of vitamin D therapy in *acne* and in *chronic arthritis* have been somewhat conflicting in opinion.

**Requirements**—Park advises that prophylactic doses in infants under a year should furnish 700 to 1000 units daily (3 teaspoonsful of *cod-liver oil*). In the second year the dosage should be at least 700 units per day. For therapy of *rickets* doses from 1000 to 300,000 units have been used. Some have advised even larger doses. Park feels that danger of overdosage is not great, although in young children the continuance of 30,000 to 50,000 units daily for more than 2 weeks might be dangerous.

Adult requirements are not known.

### Vitamin E

Although vitamin E has been discussed since its discovery in wheat germ oil in 1922, information regarding the importance of this vitamin in human nutrition has largely evolved in the past year. Synthesis was reported by Karrer and his associates<sup>146</sup> in 1938. It is now available as *ephynal acetate*, a synthetic alpha tocopherol prepared by Roche.

Earlier work on vitamin E demonstrated its importance in preserving fer-

tility and preventing abortion in animals. Human experiments by many workers have been reported since Vogt-Moller in 1933 noted the apparent value of vitamin E in humans in preventing habitual abortion. In 1940, the American Medical Association Council on Pharmacy and Chemistry stated:<sup>147</sup> "The published reports of the treatment of habitual abortion with vitamin E are sufficiently encouraging to justify further clinical experiment. Such experiments are justified only if preparations of known activity are used and if adequate diagnosis and clinical control can be established."

The value of vitamin E in *amyotrophic lateral sclerosis* and *muscular dystrophy* was first suggested by Wechsler<sup>148</sup> and Bicknell.<sup>149</sup> Stone<sup>150</sup> has reported favorable results with *wheat germ oil* in muscular dystrophy and in some cases of muscular atrophy. Spies and Vilter<sup>151</sup> also noted beneficial effects of *alpha tocopherol* in some cases of amyotrophic lateral sclerosis. This work was based on the findings of muscular atrophy and paralysis with cord changes in rats on vitamin E deficient diets. Evans<sup>152</sup> reported that wheat germ oil contains both alpha and beta tocopherols and that the alpha form probably is related to muscular atrophy while the beta form might be the antisterility factor.

**Dosage**—Present information does not permit any definite statements regarding dosage. Stone<sup>150</sup> gave capsules containing 3 minims (0.18 cc.) of *wheat germ oil*, 1 t.i.d., or the oil was given in milk or other liquid in 10 minim (0.6 cc.) doses t.i.d. In some cases the dose was raised to 1 to 1½ drams (4 to 6 cc.) daily. Wechsler<sup>148</sup> used synthetic *alpha tocopherol*, 2 tablets of ½<sub>20</sub> grain (3 mg.) each, t.i.d. Spies and Vilter<sup>151</sup> gave 7½ grains (500 mg.) of alpha tocopherol in sterile oil intramuscularly. The manufacturers recommend

¾ to 4 grains (50 to 250 mg.) of *ephynal acetate* daily for *muscular dystrophies* and *amyotrophic lateral sclerosis*. It is dispensed in ½<sub>20</sub>, ¼ and ⅜ grain (3, 10 and 25 mg.) tablets.

### Vitamin K

Since the original clinical work on the influence of vitamin K on the hemorrhagic tendency in jaundice in 1938 by Snell, Butt and Osterberg,<sup>153</sup> and Brinkhous, Smith and Warner,<sup>154</sup> the clinical importance of these discoveries has been amply demonstrated. The introduction of synthetic compounds having vitamin K properties made possible further experimental work and has increased the therapeutic usefulness of this vitamin in hemorrhagic states associated with hypoprothrombinemia.

The *causes of prothrombin deficiency* in man have been reviewed by Gordon and Sevringhaus<sup>155</sup>. They include: (1) Inadequate dietary intake; (2) absence of bile in the intestine, as in obstructive jaundice; (3) defective intestinal absorption, as in diarrhea, sprue, small bowel disease; (4) impaired liver function which makes adequate formation of prothrombin impossible even with adequate vitamin K intake; (5) in newborn infants, especially in the first 48 to 72 hours.

The present theory of blood coagulation is presented in the diagram on the following page.

**Test of Deficiency**—Most workers have used the procedures of Quick<sup>156</sup> or of Smith and his associates<sup>157</sup> as tests of blood prothrombin levels. It is generally stated that a decrease to 30 or 40 per cent of normal is apt to be associated with bleeding. Levels of 40 to 70 per cent are borderline; above 70 per cent is considered safe.

Cheney<sup>158</sup> suggests a plasma coagulation time procedure, using oxalated

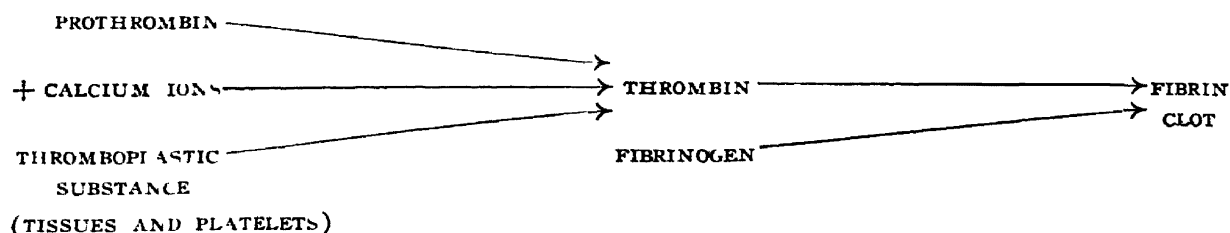


Diagram of blood coagulation (After Gordon and Sevringhaus "Vitamin Therapy in General Practice," Year Book Publishers, Chicago, Ill., 1940)

blood plasma with graduated solutions of calcium chloride. In hemophilia and in vitamin K deficiency the coagulation time is prolonged even with excess calcium.

**Treatment**—Synthetics have included products labelled  $K_1$ ,  $K_5$  and *phthiocol*, as well as several other naphthoquinones. The relative effectiveness of these compounds has been studied by Butt, Snell, Osterberg, and Bollman,<sup>159</sup> Rhoads and Fliegelman,<sup>160</sup> and others. One of the most potent synthetics, according to these investigators, is 2-methyl-1, 4-naphthoquinone (marketed by Squibb as *thylloquinone* and by Lilly as *proklot*). Of this substance  $\frac{1}{64}$  or  $\frac{1}{32}$  grain (1 or 2 mg) orally each day produces rapid return of reduced prothrombin levels to normal. Andrus and Lord<sup>161</sup> found that this same material dissolved in corn oil was effective when injected intramuscularly. In most cases a single injection of  $\frac{1}{32}$  grain (2 mg) increased blood prothrombin levels to normal (as much as 48 per cent increase). The effect of such injection may be prolonged as much as a week, according to these investigators.

Most observers call attention to the fact that occasional patients may fail to respond to any form of vitamin K therapy. It is believed that in most such instances marked liver dysfunction is present.<sup>162, 163</sup> Experimental proof of the effect of severe liver damage on prothrombin deficiency and the effect of vitamin K was obtained by Bollman, Butt, and Snell.<sup>164</sup>

Several writers have reported prothrombin deficiency which responded to vitamin K in conditions not associated with jaundice.<sup>165, 166</sup> Mackie studied the prothrombin levels of 277 miscellaneous hospital patients and found subnormal figures in 20 per cent. Most of these cases of deficiency could be explained by deficient dietary intake, deficient absorption due to intestinal disease, lack of adequate biliary secretion or to hepatic disease. It most frequently was found in ulcerative colitis, peptic ulcer, regional enteritis and pneumonia in this series.

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## HEMATOLOGY

By WILLIAM DAMESHEK, M.D.

### Blood Examination

1. **Estimation of Hemoglobin**—In recent years, the photoelectric *colorimeter* has come into increasing use for the accurate determination of hemoglobin. The clinical methods most commonly used (Sahli, Newcomer) are reasonably accurate, but even in the hands of the same technician, the variations in hemoglobin from day to day in the same patient are often great and preclude accurate work. It is for this reason that the totally objective methods of the photoelectric colorimeter are quickly becoming popularized. The Sheard-Sanford (Cenco), the Evelyn, and the Klett-Summerson types of apparatus have been tested in the author's laboratory. Of these, the Evelyn method has proved most satisfactory because of its simplicity and accuracy. The Cenco apparatus requires dilution of the blood in

a separate vessel before a special cuvette is used; this increases the time necessary for performing an estimation of hemoglobin. The Klett-Summerson method requires a separate setting of the instrument for each determination. The photoelectric methods are at present too expensive for routine office use, although in hospital clinical laboratories they are only slightly more expensive than the ordinary (and more inaccurate) DuBoscq colorimeter. In all probability, relatively inexpensive photoelectric methods will soon be available. A step in this direction is the apparatus devised by the Fisher Company. By a good photoelectric method, the percentage error is 1 per cent or less, and is thus closely comparable to that of the van Slyke apparatus. For office use at the present time, a carefully calibrated Sahli hemoglobinometer is satisfactory,

particularly if only daylight is used. A somewhat more accurate Sahli type of apparatus has recently been devised by Haden.

**2. Blood-platelets**—That the blood-platelet count may be a valuable index of bone-marrow activity is not generally appreciated. Increased regenerative activity of the bone-marrow results in an increase in reticulocytes, polymorphonuclear cells, immature polymorphonuclears, and in blood-platelets. Of these, the platelets are not infrequently the first affected, particularly in conditions in which the bone-marrow is involved by leukemic or malignant disease. Platelet counting, if done only occasionally, is apt to be quite inaccurate. For this reason, estimation of the blood-platelet level from well-made *coverslip* preparations is probably a better method for occasional use. If the platelets are present in clumps in every field, they are probably within normal limits; if they show only occasional clumps, they are probably reduced; if only 3-4 platelets are seen in each high-power field, there is definite reduction (100,000 or so); if 1-2 platelets per field are seen, the platelet count is probably about 50,000 or less per cmm.

Platelet reduction is one of the first signs in *acute leukemia*; a supposed infection with a low platelet count may well turn out to be an early case of this serious disease. Only a few infections are associated with low platelet levels; *typhoid fever*, *acute disseminated lupus erythematosus*, and *miliary tuberculosis* are examples. Extremely high platelet levels are seen in *polycythemia vera*. Platelet polycythemia ("*thrombophilia*") may be associated with so many platelets that the "*thrombocytocrit*" (determined in the hematocrit tube) may be 2 to 3 per cent (normal 0.5 per cent or less). In this condition, there is gener-

ally a very marked tendency for the development of *spontaneous thromboses*.

**3. Fresh Blood Smears**—Examination of blood-cells in an unfixed state is not often performed, except in reticulocyte counting. Dameshek<sup>1</sup> has recently shown the value of the study of *rouleaux formation*, particularly in the diagnosis of *hemolytic anemia*. In this condition, the red cells are usually thicker than normal and there is marked variation in thickness. These variations are well brought out in the type of *rouleaux* which aggregate in fresh preparations. Normal red cells aggregate in large groups like piles of coins; the cells are of approximately the same degree of thickness. In hemolytic anemias, whether congenital or acquired, many of the red cells are thicker and more spherical than normal (spherocytosis), and because of this the cells aggregate with great difficulty. The *rouleaux* become shortened and take on bizarre configurations. As the author points out, the presence of many spherical red cells—as in the more acute processes—may be likened to the appearance of a number of fat men in an elevator; in both instances, there is great difficulty in squeezing together efficiently. A glance at a fresh unstained smear of blood may thus be of value in the diagnosis of a hemolytic process, as distinct from anemia due to other causes.

*Rouleaux* formation, or red cell aggregation, is greatly increased in *infectious diseases* and in conditions associated with an increase in the serum globulin (*cf.*, *plasma-cell myeloma*). Increased *rouleaux* formation is at the basis of the rapid sedimentation rate seen in these conditions. In hemolytic processes, the sedimentation rate may become lower than normal or divided into several zones, due to the various types of erythrocytes present and the peculiar *rouleaux* which develop.



**4. Supravital Staining**—As developed by Florence Sabin and her pupils and co-workers, this consists in the examination of a fresh drop of blood which is kept warm by the use of a suitable warm chamber for the examining microscope. A drop of blood on a coverslip is allowed to fall on a slide which has been scrupulously cleansed and which contains a film of neutral red or Janus green. The preparation is then ringed with vaseline and examined in the warm chamber. Neutrophils, macrocytes, and lymphocytes have characteristic motilities and react differently to particles of the dye.

The supravital method is used almost exclusively for differential counts in some clinics but most authorities believe it has only limited value. In the author's laboratory, it is used only in the study of the very early leukocytes of *acute leukemia*. In many of these cases, it is difficult to distinguish with certainty the actual type of cell present—whether monocyte, lymphoblast, or myeloblast.

**5. Reticulocyte Staining**—This is a supravital phenomenon, in which the highly immature red cells take up the dye brilliant cresyl blue in a characteristic pattern. The reticulocyte method most commonly in use at present is the "dry" method in which (a) blood films on coverslips already stained with 0.3 per cent alcoholic (95 per cent) brilliant cresyl blue are spread and after drying are (b) counterstained with Wright's stain. With this method, permanent preparations are obtained both of the reticulocytes and of the remainder of the blood smear. The normal reticulocyte count is less than 1 per cent.

**6. Oxidase Stain**—The oxidase stain which has been found most satisfactory in the Reviewer's laboratory is that of Washburn. This method is more time-consuming than that of Sato and

Sekiya, but gives constant results with excellent staining of the oxidase positive (granulocytic or bone-marrow) cells. Two solutions are used:

#### *Solution 1*

Dissolve (1) benzidine, (2) fuchsin in alcohol. Then add nitroprusside. Solution keeps 8 to 10 months.

Benzidine base . . . . .	0.3 Gm.
Basic fuchsin . . . . .	0.3 Gm.
Sod nitroprusside (sat. aqueous sol) . . . . .	1.0 cc
Ethyl alcohol (95 per cent) . . . . .	100 cc.

#### *Solution 2*

Hydrogen peroxide . . . . .	5 to 6 drops
Tap water . . . . .	25 cc.

This solution is unstable

#### *Method—*

1. Flood blood smear with 10 drops of solution 1 and allow to stand for 60 to 90 seconds.
2. Add 5 drops of solution 2 without pouring off solution No. 1 and allow to stand 3 to 4 minutes
3. Wash with tap water
4. Flood smear while still wet with 95 per cent ethyl alcohol and allow to stand 3 to 4 minutes or until there is no more pink visible to naked eye.
5. Wash thoroughly in tap water and dry
6. Counterstain with Wright's stain, allowing the Wright's stain (and water) to remain for 30 to 45 minutes.
7. Wash briefly with tap water, flood with 95 per cent alcohol for 3 to 5 seconds, wash with tap water for 10 to 15 seconds.
8. Mount, after drying, in gum damar.

The oxidase positive granules are bluish-black.

**7. Fragility Test**—The relatively simple technic of Giffin and Sanford has been abandoned in most laboratories for the far more accurate technic of Geneva Daland and Katherine Worthley. By the latter method, accurate concentrations of hypotonic sodium chloride solutions are prepared and to them in separate test-tubes are added the same amount of 20 per cent concentration of red blood-cells. Each test is thus carried

cut with approximately the same mass of erythrocytes, whether the case is one of anemia or polycythemia.

**8. Measurement of Red Blood-cell Size**—Determination of the size of the erythrocytes has assumed increasing importance in the study of a case presenting anemia. The designations macrocytic, normocytic, and microcytic anemia are significant in relation to types of bone-marrow pathology. *Macrocytosis* indicates a maldevelopment of erythrocytes which is usually due to a deficiency in liver-extract principle (pernicious anemia); *microcytosis* usually indicates an iron deficiency state—a deficiency in hemoglobin—rather than an abnormality of red cell formation; *normocytosis* (normocytic anemia) usually indicates a disturbance in the functional capacity of the bone-marrow erythroblasts, *i. e.*, aplasia, hypoplasia, metastatic or leukemic involvement, etc. Thus, determination of the red cell size is of value diagnostically and often therapeutically and at any rate gives some idea of what to look for in a given case.

Cell size may be determined by several methods. The commonest is the *color index*, which depends on accurate hemoglobin and erythrocyte determinations. *Direct measurement* of the erythrocyte diameter with the micrometer eyepiece is an excellent method, and is preferred by the Reviewer to the less laborious diffractometric method, which gives an *average* diameter but which fails to delineate the spread of red cell size or the question of double-peaked Price-Jones curves. Schalm<sup>2</sup> gives an extensive review, in which the various methods are compared. Haden<sup>8</sup> describes a new instrument (Haden-Hausser erythrocytometer) for measuring the mean cell diameter by a diffraction method and states it is his impression that the results obtained "are even more reliable than

those obtained by direct measurement." He admits, however, that a distribution curve (Price-Jones) is not obtained. Also not stated is the fact that the method may be very misleading when many reticulocytes are present. These, being larger than the normal red cell, may give a false impression of macrocytosis ("pseudomacrocytosis" — see page 325 under HEMOLYTIC ANEMIA).

The method most commonly in use at present, however, is the determination of the mean cell volume by means of the relationship between the hematocrit and the red cell count. It is readily apparent that if a study is made of 3 cases of anemia with the same red cell count but each with a different percentage volume of packed red cells (hematocrit), the differences in hematocrit readings must be due necessarily to differences in the average size of the red cells. Thus, if the red cell count in 3 cases is 3,000,000 per cmm. and the hematocrits in the cases are respectively 20, 30, and 40 per cent, the mean corpuscular volumes in cubic micra  $\left\{ \frac{\text{Hematocrit reading} \times 10}{\text{R.B.C. count in millions}} \right\}$  are 66.7, 100, and 133; 84 to 94 c.μ is a normal figure, below 80 is microcytic, above 100 is macrocytic.

An accurate determination of the red cell count is a prime necessity. This commonly used technic, it should be noted, is subject to very definite errors, as pointed out in a careful statistically controlled study of Berkson, Magath, and Hurn.<sup>4</sup> An error of  $\pm 16$  per cent (!) is common practice when 80 small squares are counted (at a 5,000,000 red count).

**9. Bone-marrow Biopsy** — Two methods for performing biopsy of the sternal marrow are at present in general use, *i. e.*, (1) the "*open*" biopsy, using a small trephine, and (2) the *puncture method*, using a special needle, which is

similar although smaller and more rigid than a lumbar puncture needle. Favorite<sup>5</sup> has recently described an instrument which combines the trephine and puncture methods. The trephine method, as used by the Reviewer, is a surgical procedure, performed under novocaine anesthesia, in which an incision is made over the midsternum down to the periosteum; this is then incised and retracted, and the trephine\* is introduced until a sensation of "give" is obtained. The trephine is removed with a gentle "rocking" motion, carrying in its lumen a small button of bone, which is placed in Zenker-acetic acid fixative for sections. With a fine curette, bits of marrow are scraped out of the ensuing cavity in the sternum and smeared on glass slides, which are then stained with Wright-Giemsa. With this method, the topography of the bone-marrow can be visualized together with a relative idea regarding the extent of hypoplasia, fibrosis, or infiltration with leukemic or malignant cells. The method has its disadvantage, however, in that it is a surgical procedure and thus relatively formidable.

In recent years, the Reviewer has utilized the *puncture* in almost every hematological problem. Indeed, it appears that to obtain a complete picture, a puncture is essential, since it gives a good idea regarding the function of the marrow at a given moment. The puncture is readily performed in the clinic by inserting a special needle† through the anterior lamella of the sternum by a little pressure and then sucking up with a dry 5 or 10 cc. syringe a small quantity—about 0.5 cc.—of marrow material. This is spread on slides and then stained with Wright-Giemsa stain. Beautiful

preparations are ordinarily made and in about 90 per cent of the cases will give excellent information of the status of the marrow by differential counts of the nucleated red cells and the leukocytes.

The following cells are discriminated:

NUCLEATED RED CELLS	LEUKOCYTES
Erythrogon (earliest recognizable red cell form; blue cytoplasm; fine chromatic nucleus)	Myeloblast
	Promyelocyte
	Myelocyte
	Metamyelocyte
Normoblast "A" (blue-staining cytoplasm)	Mature polymorphonuclear cell
Normoblast "B" (hemoglobinous cytoplasm)	Histiocyte
	Lymphocyte
Normoblast "C" (pyknotic nucleus)	Plasma cell

In the preparations obtained by puncture, the leukocytes outnumber the erythroblastic cells by about 2:1. In former years, the Reviewer considered the trephine biopsy far superior to the puncture. This opinion has been radically altered, however, in the last few years and now the trephine biopsy is used in only about 1 case of 15. Resort is made to the trephine biopsy only if the puncture preparations fail to give adequate information or are inconclusive. In cases in which the bone-marrow is hypoplastic, sclerotic, or irregularly spotted with metastatic malignancy, the trephine biopsies usually give far greater information than the simple puncture. Storti and Borghetti<sup>6</sup> point out, however, their success in the diagnosis of metastatic tumors from sternal puncture, even when all other signs, including systematic x-rays of the bones, were negative. It may be stated that each method has its advantages and disadvantages; because of its simplicity, the puncture should be first choice, particularly for a preliminary "sampling" of the marrow.

An interesting application of the use of the puncture has been in the study of

\* This may be obtained from the Codman and Shurtleff Company, Boston, Mass.

† This may be obtained from the Hub Needle Company, Boston, Mass.

Jones<sup>7</sup> of the marrow in hyperthyroid and myxedematous states. Sternal marrow aspirated from 18 normal individuals contained an average of 6.2 per cent nucleated cells. In *hyperthyroidism*, more than twice as many cells were present, and in *hypothyroidism*, only about a third of the normal average was found. Following appropriate therapy for both conditions, there was a return to approximately normal values.

#### 10. Miscellaneous Blood Methods

—(a) *Lead*—The lead content of human blood was studied by Chalmers<sup>8</sup> by the new dithizone method of Tompsett.<sup>9</sup> The lead content of normal individuals not exposed to known sources of lead varied from 30 to 89  $\mu\text{g.}$  per 100 cc. In 44 workers exposed to lead, and without symptoms of lead poisoning, the lead content of the blood varied from 60 to 192  $\mu\text{g.}$ , the average value being approximately twice that of the normal group. The majority of these workers showed a slight degree of basophilic stippling of the red cells. In workers with typical lead poisoning, the blood lead content varied from 148 to 387  $\mu\text{g.}$  per 100 cc. Chalmers concludes that raised concentrations of lead in the blood indicate, in the same way as do stippled cells in blood films, an increased *absorption of lead* but by no means constitute definite evidence of plumbism. They provide a useful estimate of the degree of exposure to lead. The diagnosis of lead poisoning is essentially clinical. Estimations of the lead in blood have their greatest value in assessing the degree of exposure to lead in industry, so that working conditions may be such as to reduce the lead risk to a minimum.

(b) *Heparinization*—The use of heparin intravenously to prevent blood clotting has recently received great impetus through the attempts to control the infection of subacute bacterial endo-

carditis (Kelson and White<sup>10</sup>). A purified heparin for intravenous use in the human has been available for the past 2 years. It should be noted that although the 2 products are practically identical, their concentrations and unitage values differ, standardization being performed in the living cat (Connaught) and on beef plasma (Roche). It is likely that the dosage of heparin will soon be standardized in milligrams so that the question of unitage will be abolished.

The recent impetus for the use of heparin to increase the clotting time of the blood is due to the work of Best and his collaborators in the Physiology Laboratory of the University of Toronto (Best,<sup>11</sup> Murray<sup>12</sup>). Best has shown (Solandt and Best<sup>13</sup>) that heparin has 2 actions, one on the clotting time, the other on platelet agglutination, *i. e.*, in the formation of thrombi. To produce an effect on platelet agglutination requires a much larger concentration of heparin than to increase the clotting time, although to *maintain* the effect on thrombus formation requires very little added heparin once the initial effect has been obtained. McClure and Lam<sup>14</sup> recount their experiences with heparin administration in 11 cases, most of them with *postoperative pulmonary embolism*. All of them recovered. It was found that considerable individual variation in the amount of heparin necessary to elevate the clotting time was present. The clotting time of the patient's blood was maintained at approximately 15 minutes (2 to 3 times the normal value). This series is small in comparison with that of Murray,<sup>12</sup> who treated 29 patients with *pulmonary embolism*, 81 with *phlebitis*, 6 with *mesenteric thrombosis*, and 8 who were splenectomized. The Reviewer has used heparin following *splenectomy* and in the thrombotic episodes which are so common in polycythemia. Follow-

ing splenectomy, there is usually—even in cases of thrombocytopenic purpura—a tremendous increase in the platelet level, in some cases to 2 to 3 million per cmm. (2 to 3 per cent of the total volume of blood). As a result, the tendency to platelet agglutination—thrombosis—is great, particularly in the splenic pedicle. Thrombosis of the portal vein not uncommonly results, and thus what has been a successful operation may turn into a fatality. It is possible that heparinization following splenectomy may in the future be used routinely as a prophylactic measure.

(c) **Blood Volume**—A recent paper on the blood volume in miscellaneous conditions is that of Gibson, Harris, and Swigert.<sup>15</sup> In *chronic anemia*, the plasma volume is increased. The level of the hematocrit is for clinical purposes a better criterion of the degree of deficit in circulating red cell volume than either the red cell count or the hemoglobin determination. The Reviewer and his associates have recently used this method in conjunction with the *fecal urobilinogen estimation* for the determination of the "hemolytic index." The greater the red cell mass, the greater is the amount of bilirubin and urobilinogen which is produced. A large person shows a greater output of fecal urobilinogen *per diem* than a small one; an anemic person with a greatly diminished red cell mass will be expected to produce less urobilinogen than a person with a normal complement of hemoglobin. The urobilinogen output must therefore be related to the total red cell mass, which can only be determined from the blood volume. In *hemolytic anemias* (*q.v.*) the method has yielded important results.

(d) **Sedimentation Rate**—The sedimentation rate has become firmly entrenched in clinical medicine. A definite increase in rate almost always indicates

infection or malignancy, even though the evidence for this at first may not be forthcoming. It should be noted, however, that a normal rate by no means excludes one of these processes. It is universally conceded that the most accurate technic is that of Rourke and Ernstene (see article of Dorothy Rourke Gilligan<sup>16</sup>). However, the necessity for extreme accuracy in this rather "rough" procedure has been questioned. The test gives only a general idea regarding the presence or absence of increased tissue destruction, and for this reason Hambleton and Anistianson,<sup>17</sup> among others, state that changes in the direction of greater accuracy than the Westergren method are often nullified by other factors. These observers show that the Westergren method is sufficiently accurate for most purposes and state: "Alleged improvements upon the Westergren sedimentation method have been presented which appear theoretically correct, *e. g.*, correction for cell volume, the use of heparin in place of citrate, and graphic methods of recording the results. Instead of making the test more valuable, these changes have the reverse effect, either by leading to results of less clinical value, or by making the test more tedious to perform or less clear to interpret without increasing its clinical value. Hence it is recommended that the Westergren method, by reason of its simplicity, reliability, and priority, should be adopted as the standard method of performing the sedimentation test." To these statements the Reviewer heartily subscribes.

It is not too generally known that the chief factor in the sinking of the red cells is the aggregation of the individual red cells in rouleaux. The degree of aggregation depends in large part upon various factors in the serum, the most important of which appear to be globulin

and fibrinogen. Dorothy Rourke Gilligan (see above) has emphasized the linear correlation with the fibrinogen concentration. However, it is well-known that patients with high concentrations of serum globulin (multiple myeloma, etc.) have very rapid sedimentation rates, and that in infections, the degree of increase in serum globulin is often proportional to the increase in rate of sedimentation. Ropes, Rossmesl and Bauer<sup>18</sup> discuss these various factors and conclude that no absolute correlations exist between the sedimentation rate and any of the plasma-protein fractions. "The only concept which explains all of the findings is that variations in rates are due to variations in the colloidal state of the plasma with consequent changes in the electric charges on the proteins and red cells." Ham and Curtis<sup>19</sup> describe the plasma fibrinogen response, and state that elevation of this constituent is one of the most common nonspecific responses of the body to a variety of disease conditions, being comparable to such reactions as leukocytosis and hyperpyrexia.

### Blood Groups and Blood Transfusions

(a) **Blood Groups**—Wiener<sup>20</sup> presents the various pitfalls in performing blood grouping tests preliminary to blood transfusions. The international classification for blood grouping is preferred. The donor preferably should be of the same group as the patient. This is particularly important when giving a transfusion to a very anemic patient. The "universal" donor, although without *agglutinogens* in the red cells, contains alpha and beta *agglutinins* which may cause agglutinating reactions in the presence of severe anemia. High titer serum is preferable.\* The Landsteiner test-tube technic is valuable for checking

the results of the slide method, which are occasionally inconclusive. Finally, the subgroups of A and AB are discussed and a method given for differentiating A<sub>1</sub> and A<sub>2</sub> blood. In a more recent article, Wiener and Peters<sup>21</sup> describe a new agglutinin by which it is possible to divide individuals into "Rh + " and "Rh — " groups. Transfusions from an Rh + to an Rh — individual will occasionally result in agglutinating reactions. The authors point out the large number of individual differences in human blood based on the agglutinogens A<sub>1</sub>, A<sub>2</sub>, B, M, N, P, and Rh.

The M and N agglutinogens have proved exceedingly useful in bastardy cases and their use is an accepted procedure in several States. By using both the ordinary blood groups and the M and N agglutinogens it is possible to *exclude* paternity in 33 to 40 per cent of the cases tested. The methods for the preparation and use of Anti-M and N sera are fully covered in Wiener's textbook.<sup>22</sup> All individuals fall into one of the 3 categories of M +, N +, or MN +. The M and N groups have no relationship to transfusion reactions.

(b) **Blood Transfusions**—The war has immeasurably advanced the use of transfusions, blood banks, plasma transfusions, and of dried blood. White and Weinstein<sup>23</sup> cite some interesting facts regarding the use of preserved blood, and give some old and neglected references to its use. The modern use of blood banks may be said to have begun with the researches of the Soviet investigators, who were of course well equipped for mass-production methods.

DeGowin, Hardin, and Harris<sup>24</sup> report their studies on the physical and chemical changes which occur in pre-

\* This may be obtained from the Blood Betterment Association, New York City.

served blood. The factors influencing hemolysis, the marked diffusion of potassium which takes place from the red cells into the plasma, and the toxicity of blood with high values for potassium are discussed. In addition, it was determined that the preserved blood could be transfused without preheating with impunity. As the authors state: "The practice of transfusing preserved blood cold is a great convenience in conserving time and prevents untoward reactions involved in the process of heating." The prothrombin value of preserved blood decreased very gradually, reaching the 50 per cent level in about 3 weeks.

Kolmer<sup>25</sup> studied the immunologic aspects of stored blood and came to the conclusion that although the method might be useful in the treatment of acute hemorrhage and shock, its use in the treatment of anemias, blood dyscrasias, and infections was not advisable, especially after 2 to 3 days of preservation. This author points out the interesting phenomena that as early as 48 hours after collection and storage of blood, there were evidences of swelling and hemolysis of red cells; deterioration of platelets; and disintegration of leukocytes.

Wiener and Schaefer<sup>26</sup> compared the survival time in the donor's circulation of transfused erythrocytes of fresh and preserved blood. Patients receiving stored blood older than a week received cells which remained in the circulation a very short time and frequently resulted in hemoglobinemia and hemoglobinuria. They concluded that the time limit for the preservation of whole citrated blood should preferably be set at 7 days, and certainly should not exceed 10 days.

All authorities are in agreement regarding the simplicity of the citrate method. More recent developments in

transfusion technic have to do with the use of plasma and serum. As stated by Levinson, Neuwelt and Necheles,<sup>27</sup> many conditions in which transfusions of whole blood have been routinely given might well respond to the use of serum or plasma. Except in severe anemia, the red cells are of no great value in relieving the physiological pathology of shock. Even in severe hemorrhage, the sudden and marked diminution in plasma volume is the precipitating factor for the development of secondary shock. Levinson and his associates point out the inevitable delays attending the use of whole blood for transfusion, and demonstrate that pooled serum of various types may be given in massive amounts without delay, without typing, and without reactions. Serum (and plasma) may be prepared, tested, and stored in large quantities for long periods of time without deterioration; pooling partially suppresses iso-agglutinins and pooled serum may be given without regard to blood groups or compatibility. The use of large quantities of serum prevents shock even in the presence of severe hemorrhage. Serum can furthermore be kept for long periods of time and is therefore of great value in small institutions as an emergency measure. In large hospitals where blood banks are in operation, the plasma of old (7 to 14 days) blood can be salvaged for further preservation. Strumia, Wagner and Monaghan<sup>28</sup> recount their experiences with citrated plasma and confirm for pooled plasma all the various advantages enumerated by Levinson and his associates for pooled serum.

Edwards, Kay, and Davie<sup>29</sup> report on a further advance, *i. e.*, the preparation and use of *dried* plasma. These authors, too, point out that in most cases in which blood is given, it is the plasma element that produces the desired effect. This is

particularly true in wound shock, post-operative shock, and burns. It is recommended that plasma from fresh blood be used, and that it be kept in the refrigerator, although this is not absolutely essential. For drying the plasma, the authors have evolved a simple method which yields about 8 grams of dried product from 100 cc. of citrated plasma. The dried material may then be given at any time and in dilute or concentrated form, as desired. The reconstituted plasma looks exactly like the original plasma, has the same chemical constitution, and is of course ideal for war purposes, since it can be carried about in highly concentrated form at any temperature, and is instantly available upon the addition of water or normal salt solution.

### Reactions of Blood to Drugs

The reactions upon the blood of the *sulfonamide group* of drugs continue to be the subject of much comment. These drugs have an effect on hemoglobin which is usually slow but may occasionally be rapid (acute hemolytic anemia). In the slow type of response, met- and sulfhemoglobin, which are inactive pigments, are slowly formed, and are probably responsible, at least in part, for the cyanosis so commonly noted. Earlier conflicting results regarding the presence or absence of met- and sulfhemoglobin have been resolved by greater accuracy of methods. Smith,<sup>30</sup> experimenting with white rats, found that sulfanilamide given orally for a month caused small but significant amounts of methemoglobin and somewhat larger amounts of sulfhemoglobin. There was a definite reduction in hemoglobin. These results are borne out in human observations by Harris and Michel.<sup>31</sup> The degree of methemoglobinemia was proportional to the sulfanilamide concentration. Vig-

ness, Watson, and Spink<sup>32</sup> found that the cyanosis of sulfanilamide therapy is explained by the presence of methemoglobin, rarely sulfhemoglobin, and that methylene blue abolished the cyanosis as well as the abnormality of hemoglobin pigment.

Erf and MacLeod<sup>33</sup> found an increase in fecal urobilinogen output (increased blood breakdown) in cases of pneumonia treated with sulfapyridine. Three of 8 cases so treated developed a definite hemolytic anemia. Paul and Limarzi<sup>34</sup> found that the bone-marrow became more hyperplastic after sulfanilamide administration, again indicating a hemolytic effect. Spence and Roberts<sup>35</sup> report a case of extreme leukocytosis and acute hemolytic anemia with sulfanilamide administration. They correctly point out that leukocytosis may be an early hidden manifestation of a hemolytic process in association with this drug administration.

The subject of *acetanilid poisoning* receives scant attention nowadays in comparison with that of the toxic reactions of the sulfonamide drugs. Meulengracht and his collaborators (Lundsteen and Rischel<sup>36</sup>) do well, however, to revive interest in the matter, especially since drugs such as bromo-seltzer are so commonly used in this country. As with sulfanilamide, acetanilid rapidly produces cyanosis, which has for years been thought to be due to met- or sulfhemoglobin. The above authors found that the cyanosis was caused not by methemoglobin but by the decomposition of acetanilid into dark-colored derivatives of para-amidophenol. Since continuous use of the drug is followed by "a peculiar and gray addiction" with persistent fatigue and headache, the authors recommend that prescriptions for the drug should not be refilled. In this country more stringent regulations might well be made.



### Agranulocytosis

The present status of the agranulocytosis question is ably discussed by Rohr.<sup>37</sup> It is certainly queer, as Rohr points out, that in the medical clinic at Zurich, no cases of agranulocytosis were observed from 1918 to 1929, despite very careful blood studies, whereas since that time 44 typical cases have been seen. Acute, subacute, and gradually developing cases were discriminated. The allergic type was characterized by a very acute onset. The most typical clinical feature is the presence of necrotizing lesions, chiefly of the tonsils. Death was generally due to involvement of the lungs, either with "hemorrhagic edema" or gangrene. The bone-marrow in life was carefully studied. Two types of histology were seen, (1) either a cell-poor, immature promyelocytic type of marrow, or (2) a cell-rich, immature marrow. The prognosis seems to be independent of the type of therapy, but dependent chiefly on the severity of the process itself.

The many therapeutic methods, including pentose nucleotides, liver extract, transfusions, etc., are cited, but Rohr voices a healthy skepticism about all of them. This is also the Reviewer's present opinion, although it represents a change from previous views. It would seem now that if the patient's "dose" of toxic or allergic product has been overwhelming, none of the above therapeutic agents is probably of any value at all. If the patient's marrow has been only slightly, but not irretrievably damaged, recovery may ensue with treatment. Under the circumstances, it is probably wise to give some more or less logical treatment and *pentose nucleotide* seems at least moderately so.

Nordenson<sup>38</sup> studied the effects of sodium nucleinate, pentose nucleotide, and adenine sulfate on 43 normal individuals

and found that the first 2 induced a continuing peripheral neutrophil leukocytosis with hastened maturation of the granular cells of the marrow, *but only if the marrow was previously undamaged*. Since the marrow shows evidence of extreme damage in agranulocytosis, the author wonders about the value of these drugs in that disease.

The possible relationship between *agranulocytosis and leukemia* is discussed by Voth.<sup>39</sup> The difficulty in deciding between acute aleukemic leukemia and agranulocytosis in certain cases is emphasized (although it should be noted that acute leukemia always causes rapidly progressive anemia and thrombocytopenia, which are generally absent in agranulocytosis). The author believes that agranulocytosis may be the early stage and acute myelogenous leukemia a late stage of the same process. As evidence for this, he gives a (highly theoretical and not too plausible) set of 6 transitions by which agranulocytosis at the one extreme may terminate in leukemia, on the other. These speculations are quite attractive, and may have at least some foundation in fact, but it is well to remember that most cases of acute leukemia, leukemic or aleukemic, run true to type from the start with outstanding anemia and thrombopenia. At post-mortem examination they show proliferative leukemic lesions all over the body, quite the reverse of the post-mortem findings in agranulocytosis. The absence of anemia and of thrombopenia in even the most outspoken cases of agranulocytosis is quite striking.

The Reviewer has noted a frequent and rather unfortunate tendency on the part of some physicians to make the diagnosis of agranulocytosis whenever severe leukopenia from whatever cause (infection, tumor, leukemia, chemical aplasia of the marrow, etc.) is present.

True agranulocytosis is a rather narrow syndrome characterized by (1) extreme reduction in leukocytes to 1000 or less as a rule, (2) complete or almost complete absence of granulocytes, (3) by an absolute (but not relative) reduction in lymphocytes, (4) by an absence of primitive cells—myeloblasts and lymphoblasts, (5) by absence of severe anemia, and (6) a normal platelet count. As a result of the agranulocytosis, the mucous membranes develop necrotic lesions, and the patient may die of sepsis after several days of very high fever and severe constitutional manifestations.

### Infectious Mononucleosis

**Diagnosis**—The importance of this disease in general practice is gradually becoming more and more evident, as cases formerly diagnosed as “grippe,” influenza, septic sore-throat, mesenteric adenitis, appendicitis, continued fever, etc., are being recognized as cases of infectious mononucleosis. That the disorder frequently, if not usually, goes unrecognized is by now a truism. If the practitioner were to examine carefully for enlarged lymph-nodes and spleen in every case of fever, the percentage of recognized cases would be greatly increased. Too often, it would seem, the throat, heart and lungs, and abdomen are examined without any attention at all being paid to possible lymphadenopathy. In the future, or perhaps even now, if blood smears were made of every case with fever, diagnosis of the disease would, it is felt, be made quite often. The blood picture is so characteristic, once it is known and recognized, that it permits of ready diagnosis. There is *lymphocytosis* (not monocytosis), the lymphocytes being of all possible sizes, shapes, and staining characteristics. Great variability in the type of lymphocyte is the outstanding feature—quite the

reverse from acute leukemia in which a “monotonous” blood picture with 1 type of lymphocyte, usually the lymphoblast, predominating. There is furthermore no anemia, and hardly ever any reduction in blood-platelets—again quite in contrast to acute leukemia in which rapidly-progressive anemia and thrombopenia are quite the rule. The introduction of the heterophile agglutination test has been of material aid in further defining these cases, which usually give a positive agglutinating reaction with sheep red blood-cells.

There is almost no limit to the bizarre manifestations given by this disease. Like all diseases which are generalized (polycythemia, metabolic disorders, etc.), peculiar localizations will occasionally crop up. Jaundice, which looks typically like catarrhal jaundice, may be the presenting symptom. A case of this type, associated with a positive Wasserman reaction, is reported by Fowler and Tinrick<sup>40</sup>; as these authors point out, “it is not improbable that many cases diagnosed as catarrhal jaundice have actually been infectious mononucleosis.” Positive serological tests for syphilis not infrequently occur concurrently with the positive heterophile reaction. Alan Bernstein,<sup>41</sup> who gives a comprehensive review of the disease, found in 44 cases a transitorily positive Wassermann reaction in 8 instances. These are generally evanescent and usually disappear in 2 to 3 weeks. The Reviewer has observed this phenomenon only twice in approximately 200 cases, but it must be admitted that frequent serological tests for syphilis were not made, as in Bernstein’s material. Israel M. Davidsohn (Chicago) who has been responsible for some of the outstanding work with the heterophile reaction has failed, however, to find 1 case with positive serological tests for

lues in his carefully studied series (personal communication).

Bernstein, in his review, cites various symptoms such as edema of the eyelids, skin eruptions, central nervous system manifestations, etc., which are not generally connected with the disease but which are not infrequently present. It should be made the rule in every case of continued fever to search the blood smear carefully for evidence of abnormal lymphocytosis, and to do the heterophile reaction. Templeton and Sutherland<sup>42</sup> point out the frequency of an exanthem in the disease—17 of 91 cases. In 12 cases, the rash was practically indistinguishable from that of German measles. In this connection, it should be noted that the latter disease is associated with well-marked lymphadenopathy and not infrequently with an abnormal lymphocytic reaction in the blood and one wonders whether they might be related.

**Etiology**—This remains obscure, as well as the manner of spread. Epidemics are occasionally seen, but even in these, the type of spread has not been worked out. Because of the absence of autopsied material, the pathology of the disorder has naturally not been extensively studied. Biopsied lymph-nodes have resulted, however, in an understanding of the fundamental nature of the lymphocytic proliferation. Gall and Stout,<sup>43</sup> on the basis of 10 biopsied lymph-nodes, claim that there is a specific pathological picture. This is characterized by (1) marked proliferative activity of the pulp, (2) extensive but focal proliferative activity of "clasmatocytes," and (3) the appearance of large numbers of "specific" "infectious mononucleosis" cells. These are large lymphocytes with abundant basophilic cytoplasm, which with phloxin and methylene blue stains have a filmy blue quality of the cytoplasm.

**Prognosis**—This is always good.

**Treatment**—There is no specific therapy for the disease, which indeed requires only *symptomatic treatment* as a rule. The sulfonamide drugs are of no value unless there is a secondary infection with streptococci or pneumococci. Occasionally, there is a rather severe and associated *Vincent's infection* which may cause a rather nasty cervical adenitis. If this is present, an injection of *neorsphenamine* 5 grains (0.3 Gm.) intravenously may be of striking benefit.

### Anemia

**Iron Deficiency Anemia—Hypochromic Anemia**—Out of the wastebasket of "secondary anemia," which term the Reviewer considers meaningless, since all anemia is secondary, has been pulled a group of cases of "idopathic" or "primary" hypochromic, iron deficiency anemias. These are characterized by chronicity, low hemoglobin values, with relatively normal erythrocyte counts, usually achlorhydria, and a number of physical features due in all probability to effects on body cells of chronic iron starvation. These features are graying of the hair, wrinkling and flabbiness of the skin, atrophy of the tongue, cheilosis, and flattening and brittleness of the finger nails. Although these cases are ordinarily described in adult females above the age of 40, they probably start early in adult life, even at the time of puberty, when chlorosis may be disguised. It is also not unlikely that many of the cases of so-called nutritional anemias of infancy belong in this group.

Chronic iron deficiency anemia is the end-result usually of a group of etiological factors, *i. e.*, a diet inadequate in iron, achlorhydria, malabsorption of material from the bowel, hemorrhage (menorrhagia, hemorrhoids, etc.), multiple pregnancies, etc. Rarely is a single factor alone at the bottom of any of these cases,

although it must be stated that achlorhydria may be at the heart of the problem. Thus, cases with impaired dietary, menorrhagia, etc., might develop very little anemia *unless* the gastric juice too was affected.

Iron deficiency anemia *in children* is discussed by Abbott and Ahmann,<sup>44</sup> who studied a group of 883 rural school children in Florida. Half of these children were anemic (below 70 per cent hemoglobin, Dare), and 31 per cent between 70 and 85 per cent hemoglobin. A number of children had been born of anemic mothers and had probably been anemic to some extent for the greater part of their lives. Pallor, general muscular weakness, faintness, and lassitude, and a faint systolic murmur were commonly present when the hemoglobin level was below 50 per cent. As etiological factors are listed poverty, food high in carbohydrate, hookworm infestation, and various gastrointestinal disturbances. It is also possible that certain infants born in families with either pernicious anemia or chronic hypochromic anemia may have a constitutionally defective gastric mucosa which might result in failure to digest adequately organic iron-containing foods.

By the use of radioactive ("tagged") iron, P. F. Hahn, J. F. Ross, W. F. Bale, and G. H. Whipple,<sup>45</sup> coworkers at the University of Rochester, have been actively engaged in the study of iron metabolism. In animals, it is possible to study the labelled iron from the time it enters the circulation until it is excreted. The dog with chronic iron deficiency takes up iron into its red blood-cells in a very few hours, and the body-cells are apparently avid for it, whereas the plethoric animal rejects injected iron. In the individual who has had a hemorrhage, as from a peptic ulcer, it has long been debated whether added iron was of

value. Lyons and Brenner<sup>46</sup> contribute to this discussion through an analysis of 237 cases of bleeding peptic ulcer. The rate of erythropoiesis after hemorrhage appeared strictly dependent on the degree of anemia, and was "fully as good as that reported for patients treated with a liberal 'puréed diet' and iron." Transfusion itself appeared to have no effect on the rate of red cell production.

In *pregnancy*, the incidence of anemia is quite high, amounting, Bethell, Gardiner and MacKinnon<sup>47</sup> state, to 54 per cent of 158 cases studied. The majority of cases studied were iron deficiency in type. Since normal gestation places no great demand on maternal iron stores, the anemia was due mostly to other factors: (1) Low iron reserves; (2) restricted utilization of reserve iron, (3) impaired absorption of iron during gestation, and (4) low dietary intake of iron. It should be noted that poverty and an inadequate intake of food iron frequently go together, since the foods containing large amounts of iron are for the most part the most expensive (meat, liver, green vegetables, eggs). If inorganic ferrous preparations are given in cases of hypochromic anemia, there is an excellent response; the routine use of iron during pregnancy is a justifiable procedure.

In *males*, chronic hypochromic anemia is almost always due to persistent bleeding, particularly from the gastrointestinal tract. Given a case of apparently idiopathic hypochromic anemia in a male, the stools should be searched for occult blood and gastrointestinal studies instituted. Not infrequently, herniation of the stomach is discovered. A number of cases have been reported in recent years, 2 having been reported recently by Dyke and Dyas.<sup>48</sup> In the second case, occult blood in the feces was present,

although it was negative in the first case. Occult blood in the stools is usually absent in these cases, and the anemia thus is probably due to bleeding in the past.

Recently, the possibility that some types of vitamin deficiency might be linked with hypochromic, microcytic anemia has been entertained. Thus, in dogs, a deficiency in the "rat antidermatitis principle"—vitamin B<sub>6</sub> or pyridoxin—has been shown by Fouts, Helmer and Lepkovsky<sup>49</sup> to result in this type of anemia, which responds to B<sub>6</sub> administration. This has been confirmed by Borson and Mettier.<sup>50</sup> Whether these experimental observations have any relationship to the hypochromic anemia of humans is questionable.

**Chlorosis**—From recent studies, it would seem likely that familial or constitutional atrophy of the gastric mucosa may occur. When present, it may lead to so-called nutritional anemia in infancy, to chlorosis at puberty, and to so-called idiopathic hypochromic anemia of late adult life. Certain cases may furthermore develop pernicious anemia as a late manifestation. The marked reduction in hemoglobin which ensues with iron deficiency results in a disappearance of the normal healthy red color from the skin, with the result that the basic yellowish color of the skin becomes quite obvious. Due to a common tendency in medicine to exaggerate colors, the yellowish coloration has been called "green," possibly because greenish "overtones" may be seen by the more artistic observers. The "green sickness" chlorosis is thus simply a chronic iron deficiency state of young people, usually young women, who have an atrophied gastric mucosa. In the Reviewer's series, complete achlorhydria is the rule, despite the few observations in the very old literature to the contrary. Most of the signs of chronic iron deficiency in

addition to the pallor are present when the patient is observed: Glossitis with atrophy of the tongue's musculature; cheilosis, flattening of the finger-nails, etc. Response to *inorganic iron* is rapid, but relapses occur when the medication is discontinued, so that a maintenance dose is recommended.

It is suspected by the Reviewer that true chlorosis is not extinct, but that most of the diagnoses of that condition before 1900 were made without benefit of blood examinations. For this reason, many cases of "pseudo-anemia," and many instances of various diseases such as pulmonary tuberculosis, subacute bacterial endocarditis and the like were diagnosed as chlorosis. Nowadays, the disorder is relatively uncommon but by no means extinct.

**Pernicious Anemia**—This is a deficiency disease. As such, it may result from an inadequate diet, a lack of digestion of protein by an atrophied gastric mucosa which fails to produce "intrinsic factor," malabsorption by the bowels, hepatic disease (inadequate storage), or from loss of liver extract substance to the fetus. More recently, the possibility of lack of utilization of liver extract substance by the body ("achrestic anemia") has been postulated. It should be noted that in a given instance, a number of etiological factors may operate together. Thus, both the diet and the intrinsic factor may be grossly deficient; if only one were deficient, the patient might not develop the deficiency state. Multiple etiological factors are thus important, and it should also be noted that the changes in the body which result are also multiple. Pernicious anemia is not only "anemia"; it is a generalized disturbance—a starvation of the body for liver extract substance, with the result that graying of the hair, glossitis, gastrointestinal manifestations, and central nervous system

disturbances result. The anemia is simply 1 aspect of the deficiency, resulting from lack of liver extract substance by the bone-marrow cells

The constitutional nature of pernicious anemia is brought out in an article by Schemm<sup>51</sup> in which 5 authenticated cases in the same generation of 1 family were studied. In addition, 2 cases in each of 5 families have been studied. It is likely that all of the hereditary cases are based on an inherited gastric mucosal atrophy with resultant diminution or even complete lack of "intrinsic factor." Schindler, Kirsner and Palmer<sup>52</sup> discuss gastroscopic observations in the disease. Histologically, atrophic gastritis is chiefly characterized by extreme thinness of the gastric mucosa due to disappearance of the gastric glands. Schindler and his coworkers believe that the various changes are the end-result of chronic inflammation, although most observers believe they are degenerative. A certain parallelism between changes in the tongue, the mucosa of the stomach, and the spinal cord is usually present, although occasionally the gastric mucosa may be atrophied with changes of the tongue, the blood, or the nervous system. Treatment with *liver extract*, *iron*, and *vitamin B complex* was instituted in 8 cases with atrophic gastritis without other abnormalities with the result that in 3 cases the mucosa returned to an apparently normal status.

For pernicious anemia to develop in a given case, there must either be a great reduction in extrinsic factor with only slight reduction in intrinsic factor, or an extreme reduction in intrinsic factor alone, or a reduction in both factors. In most cases, it is likely that the 2 factors are both diminished, since many patients with gastric atrophy probably never develop the disease pernicious anemia unless and until the diet (particularly pro-

tein) becomes greatly impaired. Pure cases of dietary deficiency alone causing the pernicious anemia syndrome are rare in temperate climates, although they are said to be much commoner in the tropics. Alsted<sup>53</sup> reports a case of "exogenous" pernicious anemia, an individual on an extremely inadequate diet who nevertheless had free HCl in his gastric juice, and who responded completely to "extrinsic factor" alone.

"*Achrestic*" anemia has been described for the third time by Israels and Wilkinson.<sup>54</sup> In their first papers, the authors described these cases of apparently typical pernicious anemia with typical megaloblastic bone-marrow but which failed to respond to liver extract. Another peculiar feature was the presence of small quantities of free HCl in the gastric juice. Because the liver of some of these autopsied patients contained potent liver extract substances, it was postulated that liver extract could not be *utilized* by the body. In the present article, the former concepts of the condition have apparently been somewhat altered, for 6 cases are reported which seem to be quite typical of pernicious anemia in every respect except that the gastric juice contained free hydrochloric acid. *All of the cases* responded more or less well to the administration of either *liver extract*, *gastric extract*, or both substances, although in several the response was rather slow. The bone-marrow was typically megaloblastic in all cases. Since all the cases responded more or less well to liver extract, it is difficult to see how they could be classified as "achrestic." The question of presence or lack of intrinsic factor in the gastric juice was not studied, although it would seem that this was of greater fundamental importance than the presence of free HCl, since Castle showed some years ago that

intrinsic factor may be lacking even in the presence of free HCl.

That there is a condition such as achrestic anemia—in reality a subtype of pernicious anemia—is likely. The Reviewer recently observed such a case, in which, although every feature of pernicious anemia was present, 2 features were unusual, *i. e.*, (1) the presence of free HCl, and (2) the great refractoriness to liver extract. Only when large doses of *ventriculin* were given did the patient begin rapidly to improve.

*Sprue* is probably another subtype of the larger pernicious anemia syndrome. Castle and his coworkers have considered that the 2 diseases are identical, and it cannot be doubted that histologically and hematologically they often cannot be told apart. Rodriguez-Molina<sup>55</sup> found that the bone-marrow and hematological aspects of sprue were identical with pernicious anemia. On the other hand, it cannot be denied that extremely bulky stools rich in fat, a low blood calcium, increased sugar tolerance, and a low rather than a high fecal urobilinogen output are characteristic of sprue and not of pernicious anemia. It is probable, however, that these are *special* symptoms perhaps representing, as stated above, a subtype of the larger syndrome. The matter of the fecal urobilinogen output is receiving increasing attention. It is the most sensitive method available for the determination of the degree of blood destruction. In pernicious anemia there is always an increased output of urobilinogen in the feces. In sprue, however, as pointed out by Koller,<sup>56</sup> the output, as measured in 3 cases, was less than normal.

The duration of the *remission* in pernicious anemia has recently been studied by Strauss and Pohle.<sup>57</sup> The following important conclusions are drawn: (1) Patients with pernicious anemia who re-

quire relatively little *liver extract* to maintain a normal blood level may relapse in as short a time as 2 months after liver therapy is omitted; (2) the majority of patients with pernicious anemia cannot be satisfactorily treated by the use of massive doses of liver extract given at intervals of several months; (3) the optimum interval between injections for most patients with pernicious anemia is from 1 to 4 weeks.

Another article dealing with therapy, also by the same group, is that on continued degeneration of the spinal cord with results of 7 years' experience with *parenteral liver therapy* (Strauss, Solomon, and Fox<sup>58</sup>). It was found that the neural lesions could be *arrested* in every case. If adequately treated, no case of pernicious anemia developed new neurologic disturbances. As regards adequate therapy, (1) the blood values must be maintained at R.B.C. of 4,500,-000 or over, the color index at 1.0 or below, and the mean corpuscular volume below 100 c. $\mu$ ; (2) there must be no symptoms of any nature (glossitis, indigestion, etc.) attributable to pernicious anemia; (3) if there is recurrence of paresthesias or other subjective disturbance, the dose of liver extract must be doubled. Each patient's dosage is an individual matter. The material used by Strauss and his coworkers was a very dilute liver extract (1 unit per cc.) usually given in 2½ drams (10 cc.) amount weekly, although some patients required the material 3 times weekly. In the Reviewer's experience, the highly concentrated extracts are just as effective in treating the neurologic lesions of pernicious anemia as the crude extracts.

**Hemolytic Anemias**—Interest in this group of cases, which are characterized by increased blood destruction, has developed considerably in the last few years. Dameshek and Schwartz,<sup>59</sup> in

discussing acute hemolytic anemia, classify the hemolytic anemias as follows:

- A. Congenital hemolytic icterus (anemia):
  - 1 Chronic, with or without crisis
  - 2 Subacute
  - 3 Acute (crisis)
- B. Acquired hemolytic icterus (anemia):
  - 1 Secondary to known cause (infectious, chemical, "toxic," pregnancy, etc.)
  - 2 Symptomatic, in association with certain, usually malignant diseases, as lymphatic leukemia, Hodgkin's disease, carcinomatosis
  - 3 Of unknown cause, with or without hemolysins in the serum:
    - (a) Chronic, with or without crisis
    - (b) Subacute
    - (c) Acute
    - (d) Acute fulminating, often with hemoglobinuria

This classification attempts to restore the former well-known grouping of congenital and acquired types, especially since the latter grouping has been for some reason frowned upon. There has been an unfortunate tendency to put almost every case of hemolytic anemia into the congenital variety, whether or not a familial history was discernible. It is the contention of Dameshek and Schwartz that spherocytosis and increased hypotonic saline fragility are by no means pathognomonic of the congenital variety, but may occur in every type of hemolytic process.

1. **Spherocytosis**—The spherocyte is at the crux of the situation. About 20 years ago, Naegeli pointed out that the red cells in congenital hemolytic jaundice tended on the whole to be smaller, rounder, and thicker than normal and he designated them as spherocytes. He believed that the disorder represented an abnormal production of cells in a faulty bone-marrow, and that the spherocyte was the pathognomonic cell of the hereditary disease. This statement was universally accepted. In recent years, R. L. Haden and others found that there was

a direct correlation between the degree of thickness of the erythrocyte and its fragility to hypotonic solutions of sodium chloride. More recently, Dameshek and Schwartz found hemolysins in the serum of 2 cases of acutely developing hemolytic anemia, and in 1 of the cases there was marked spherocytosis. As the patient recovered after splenectomy, the hemolysin disappeared and spherocytosis gradually diminished and disappeared, and the saline fragility became normal. These authors reasoned that perhaps the hemolysin and the spherocytosis were related. They therefore produced a hemolytic serum which, when injected in guinea-pigs, resulted in acute or subacute hemolytic anemia, spherocytosis, increased fragility, reticulocytosis, etc. The degree of spherocytosis and anemia varied directly with the amount of hemolytic serum injected. The bone-marrow was normal. These observations have recently been confirmed by Tigertt and Duncan.<sup>60</sup> Thus, it was shown for the first time that spherocytosis could be produced without postulating an abnormal bone-marrow. Spherocytosis in these experiments was shown to be the end-result of the activity of hemolysin and the possibility was broached that a spherocyte represented a red cell which had already been damaged by a hemolytic agent which could either be demonstrated or not. *The spherocyte is the forerunner of hemolysis.* It can be produced by immune hemolytic sera, by various chemicals such as sulfanilamide, by hypotonic salt solutions, in fact by many agents which damage the red cell by various means. Although spherocytes of various conditions are morphologically indistinguishable, they may be quite different from the chemical or physical standpoints.

2. **Hemolysins**—Because of the finding of hemolysins in a few cases of hemo-



lytic anemia, because hemolysins produce various types of hemolytic syndromes experimentally, and because hemolysins result in spherocytosis, it has been the contention of Dameshek and Schwartz that they are at the basis of many of the hemolytic syndromes. Other types of hemolytic syndromes have been found in association with such conditions as paroxysmal (cold) hemoglobinuria, etc. However, other theories postulate quite different mechanisms. That of an abnormal bone-marrow producing spherocytosis is well-established, although there is no evidence to indicate that this actually occurs. In fact, recent studies of Dameshek and his co-workers have demonstrated that the erythrocyte production in the bone-marrow is quite normal.

Ham and Castle<sup>114</sup> have recently stressed the importance of intravascular stasis as a prime cause of increased blood destruction. They point out that the spleen is primarily a stasis organ, and that splenectomy is beneficial because the abnormal spherocytes can continue unhampered in the circulation with the hemolyzing effects of continued stasis in the spleen. They claim that increased agglutination (rather than hemolysis) is at the bottom of the experimental results of Dameshek and Schwartz, and show that a so-called pure agglutinin (concanavalin-A) produces hemolytic anemia in animals. They point out many clinical applications of these 2 ideas of agglutination and stasis as the prime causes of hemolytic anemia. Although the speculations of Ham and Castle may in certain respects be correct (agglutination hemolytic transfusion reactions; auto-agglutinins, etc.), they do not explain the lack of increased hemolysis in polycythemia—in which stasis is extreme—nor in thrombosis of the splenic vein.

The relationship of the *spleen* to increased hemolysis is still quite obscure. Ham and Castle postulate for the spleen a simple physical or "passive" function; they state that blood incubating in a test-tube is identical with blood present in the splenic sinusoids. There is a possibility, however, that the spleen participates more "actively," perhaps through obscure cellular mechanisms. After all, the spleen is something more than a test-tube. The dramatic effects of splenectomy in many cases of hemolytic anemia are much in favor of this idea, especially in the acquired cases, when there is frequently a complete reversion of the blood picture to normal. Thus, the theory of "hypersplenism" or of hyperactivity of the entire reticulo-endothelial system must be considered, at least in some cases.

In summary, it is likely that various mechanisms are responsible for the development of hemolytic processes. The hemolysin theory seems on the whole to be most satisfactory, since it helps to explain the majority of cases. It must be conceded, however, that agglutinative phenomena will lead to hemolysis, and that simple passive stasis in the spleen may help in the full development of a hemolytic process. Hemolysin production by an abnormally active spleen probably is at fault occasionally. R. L. Haden,<sup>61</sup> in an admirable review of hemolytic anemia, states that the 2 factors in increased hemolysis may be summarized as follows:

I. Increased hemolysis of normal cells damaged by foreign agents:

- (a) Chemicals
- (b) Parasites
- (c) Bacterial toxins
- (d) Amboceptor and complement reactions (including hemolysins and agglutinins)

II. Increased activity of the spleen.

The subject of *pathogenesis* is still in the process of elucidation, and the final word has certainly not been said.

3. **Clinical Studies**—Farrar, Burnett, and Steigman<sup>62</sup> found an hemolysin in a case of acute hemolytic anemia which was cured by *splenectomy*, thus confirming the observations of Dameshek and Schwartz.<sup>59</sup> Another case of acute hemolytic anemia with spherocytosis with recovery after splenectomy is reported by Mandelbaum.<sup>63</sup> This case is of interest in that it occurred in an individual 75 years of age. It also illustrates to what length writers will go to avoid the designation of acquired hemolytic jaundice. Since spherocytosis was present, a *congenital* hemolytic process was assumed, even though the patient was 75, had no familial history, and had never previously been known to have had either splenomegaly, anemia, or jaundice. It should be continually stressed that spherocytosis is by no means pathognomonic of the congenital type, as the author states.

In a study of a case of typical *hereditary hemolytic jaundice*, Waugh and Lamontagne<sup>64</sup> make some interesting observations of the types of bilirubin present and of the hypotonic fragility of the erythrocytes. These observations are both carried out utilizing the photoelectric colorimeter of Evelyn adapted to bilirubin and fragility measurements. Even in hemolytic icterus, a small amount of "direct" bilirubin can be found by the technic of Malloy and Evelyn. The hypotonic fragility as determined with the photoelectric colorimeter can be determined very accurately and will show very small degrees of hemolysis. With this technic Waugh and Lamontagne demonstrated that before splenectomy a small number of extremely fragile erythrocytes is present, disappearing after operation.

Careful and well-conceived studies of a rare type of hemolytic syndrome, *i. e.*, "*paroxysmal nocturnal hemoglobinuria*," is that of Ham<sup>65</sup> and of Ham and Dingle.<sup>66</sup> Although the fundamental abnormality was found to reside in the red blood-cells, a thermolabile factor essential for hemolysis was found in the serum of all the 5 cases examined. The hemoglobinemia and hemoglobinuria were associated with sleep, and it is suggested that during sleep there is an increased intravascular hemolysis associated with increased acidity of the blood, especially of regions of the blood subject to stasis, such as the spleen. Further detailed studies bearing on the immunological situations involved are described in the second of the 2 articles.

Dameshek and Schwartz contribute a review of all the cases of acute hemolytic anemia (*acquired hemolytic icterus, acute type*). Many of these have been miscalled *Lederer's anemia*, although identical cases were described many years ago by Widai and his collaborators and by Chauffard. These cases are characterized by acute or subacute onset, rapidly progressive anemia, jaundice without bile in the urine and the increased output of urobilinogen in urine and feces, and a variable blood picture. The anemia is normocytic as a rule, but either spherocytes or reticulocytes may dominate the picture. If the first, the red cells are small and hypotonic fragility is greatly increased; if the second, the red cells look large and the fragility is only slightly altered. The concept that these cases are benign and respond to 1 or 2 transfusions has for some reason persisted; the reverse is frequently true. Several transfusions are given and the patient may fail to respond. That splenectomy is often followed by a dramatic effect is ignored. Since the concept that splenectomy is of no value in

these cases has become ingrained, the patient may die without the probable benefit of this operation. Not all cases recover following splenectomy, which indeed is a serious procedure in the age group of these patients (usually from 40 to 65). The Reviewer's routine at the present time is to give 1 to 3 *transfusions*; if no definite therapeutic effect has taken place, *splenectomy* is performed. If this procedure is postponed, the patient may develop new hemolysins or agglutinins, have severe transfusion reactions, etc., and succumb to a final last-ditch operation.

*Cooley's erythroblastic anemia* is receiving increasing attention. This is a disease which is found chiefly in Greeks and Italian children, and which is characterized by hemolytic anemia, the presence of large numbers of nucleated red cells and bone changes. The latter are due in all probability to marked hyperplasia of the bone-marrow. Both Dameshek<sup>67</sup> and Smith<sup>115</sup> described a "new" abnormality of the red cells in this disorder, namely, the target cell. This cell, which is the antithesis of the thick spherocyte, is a very thin red cell, which has the appearance of a bull's eye or target in stained smears and which is unusually resistant to hypotonic salt solutions. It may well be the inherited factor in Cooley's anemia. Dameshek described a "new" condition under the heading of "*target cell*" anemia, which is characterized by bone changes like those of Cooley's anemia, increased blood destruction, and presence of many target cells, with increased resistance to hypotonic salt solution. These cases are important in that they probably represent mild cases of Cooley's anemia which may reach adulthood and result in the dissemination of the more outspoken disorder of Cooley's anemia. Under the designation of "a familial hemopoietic

disorder in Italian adolescents and adults resembling Mediterranean disease (*thalassemia*)," Wintrobe, Matthews, Pollack and Dobyns<sup>68</sup> describe a number of such cases. The term "target cell" was first used by Barrett. It is seen following splenectomy, in obstructive jaundice, certain hepatic diseases, in Cooley's anemia and in sickle cell anemia. Because of its increased *thinness*, it can absorb more water than a normal erythrocyte and thus is less susceptible to bursting in hypotonic salt solutions.

"*Leuko-erythroblastic Anemia*," "*Myelophthisic Anemia with Leukemoid Blood Picture*," etc.—In recent years, there has developed an increasing interest in a condition which is characterized clinically by (a) slowly progressive anemia, (b) leukocytosis with the presence of myelocytes and metamyelocytes, (c) presence of a variable number of nucleated red cells, (d) splenomegaly, and (e) bone changes and histologically by myeloid transformation of the spleen (ectopic bone-marrow activity in the spleen) and a sclerotic bone-marrow. Thompson and Illyne<sup>69</sup> bring out in brief all the important points: (1) Replacement of the bone-marrow by foreign tissues (fibrosis, new bone, carcinoma, etc.) will result in the above hematological findings, characterized by *some* myelocytes, a *disproportionate* number of normoblasts, and a reduction in blood-platelets. These cases occur most commonly as a sequel of polycythemia—the spleen remains very large, anemia gradually develops, and myelocytes and normoblasts appear in the blood. They may also occur with *any* condition in which the bone-marrow is replaced by foreign tissue. The spleen then tries to take over the functions of the marrow with more or less success. It is important to differentiate these

cases from chronic myelogenous leukemia. This can be done best by performing a *trephine* bone-marrow biopsy (punctures are of no value in this condition) which shows usually fibroblastic proliferation in the marrow. X-ray therapy and splenectomy are of no value.

### Bone-marrow Reactions Due to Benzene

Hunter<sup>70</sup> showed that prolonged exposure to benzene may result in anemia, leukopenia, or thrombocytopenia either singly or together (aplastic anemia), or in polycythemia, or leukemia. Mallory, Gall and Brickley<sup>71</sup> describe the histological material of the same group of cases. Hyperplasia—even leukemic—may follow prolonged exposure and hypoplasia, either short or long contact. This is an important article from the standpoint of industrial disease for more and more cases of leukemia are being seen following exposure to benzene or closely related chemicals used in industry.

### Polycythemia Vera

**Symptoms and Diagnosis**—This disease of unknown origin is characterized by extensive proliferation of the entire bone-marrow with the result that the red cells, leukocytes, and platelets become greatly increased in the peripheral blood. The great increase in circulating red cell mass results in the establishment of a very viscous, slow-moving circulation. The combination of a greatly distended blood volume and a tendency to multiple thromboses accounts for the majority of the symptoms of the disorder, which are described by Dameshek and Henstell.<sup>72</sup> These authors point out that the multiplicity of symptoms may result in the diagnosis of psychoneurosis, or of 1 set of symptoms is outstanding in such diagnoses as nephritis, cardiovascular disease, mi-

graine, peripheral vascular disease. All the organs of the body are widely distended with blood, thus accounting for the widespread symptomatology. In addition, the platelet count is usually extremely high and with the sluggish circulation and the increased blood viscosity, thrombotic manifestations are common. These commonly occur in the extremities, simulating thromboangiitis, obliterans, but not infrequently are present internally. Thus, cerebral thromboses, coronary thrombosis (*cf.* H. R. Miller<sup>73</sup>), hepatic vein thrombosis, portal vein thrombosis, etc., may occur. Many cases go about unrecognized for many years, being treated for menopause, migraine, heart disease, etc. It should be the rule to do a red cell count (not Tallquist hemoglobin) in any individual, who by his plethoric appearance may cause polycythemia to be suspected. Further clinical diagnostic aids are distended retinal veins, spleno- and hepatomegaly, and flushed mucous membranes. The erythrocyte count usually gives the diagnosis, although in doubtful cases the hematocrit, blood volume, leukocyte and platelet counts, etc., are all necessary.

Most cases go along for many years in various degrees of discomfort. The development of the degenerative diseases is accelerated and death is usually the result of nephritis, coronary disease, cerebral accidents, etc. In 3 of the Reviewer's 40 cases, anemia gradually developed in association with leukocytosis, presence of immature granulocytes and nucleated erythrocytes. Are these cases chronic myelogenous leukemia or do they represent fibrosis of the marrow with myeloid metaplasia of the spleen? Most observers have considered that the polycythemic condition became transformed into leukemia, but it now becomes increasingly apparent that these cases are not truly leukemic, but that

the blood picture is simply "leukemoid" in type in association with a fibrotic bone-marrow and a spleen which is actively attempting to produce bone-marrow cells. It is likely that the majority of the cases of "leuko-erythroblastic anemia" (*q.v.*) have previously been unrecognized examples of polycythemia.

**Treatment**—The best treatment for polycythemia is still being debated. X-ray therapy over bones (and marrow), phenylhydrazine, treatment with Fowler's solution or with radio-active phosphorus have all been advocated. Potentially or actually all of these methods are dangerous. In the Reviewer's hands, the production of an iron-deficiency state has proved safe and therapeutically effective. *Venesections* of 500 cc. of blood are performed twice weekly until the hemoglobin is reduced to approximately 80 per cent and the erythrocyte count to approximately 5,000,000. This usually takes 6 to 8 venesections. The patient is then placed on an *iron-low diet* restricting meats, liver, eggs, green vegetables, and rye bread. The combination of a great loss of iron (hemoglobin), together with a continued low intake of iron results in a sustained iron-deficiency state with relatively low values for hemoglobin. The erythrocyte count under this regimen gradually rises to 7,000,000 to 8,000,000, but with the iron deficiency, the values for hemoglobin, hematocrit, and red cell mass remain down for periods of 6 to 12 months (average 8 months). The method is safe and physiological and requires but little supervision after the first series of venesections. Estimations of hemoglobin and hematocrit percentages become of far greater value than erythrocyte counts.

### Leukocytic Proliferations

**Leukemias**—The marked proliferation of 1 of the 3 tissues which produce

leukocytes (bone-marrow, lymphoid system, reticulo-endothelial system) results in the production of large numbers of white blood-cells which overrun all the various organs. The bone-marrow particularly suffers because of the great interference with erythroblastic and platelet production. If the process is highly malignant, it is clinically "acute"; if relatively benign, it is "chronic" and may last for years without causing too much disturbance to the bodily economy.

**Diagnosis**—Mouth lesions are common in acute cases, and are particularly striking in the monocytic type. Dental extractions are frequently performed for aching gums. Unexplained leukocytosis may be the first and even the only sign of chronic myelogenous leukemia, as Wintrobe and Hasenbush<sup>74</sup> point out. A distinct lymphocytosis, even with a normal total leukocyte count, was an early sign in several cases of the chronic lymphatic variety and early anemia was often present. A number of atypical manifestations of leukemia are described by Wintrobe and Mitchell,<sup>75</sup> cases simulating infections such as brucellosis, osteomyelitis, and subacute bacterial endocarditis. Bone pains, bone lesions, unusual skin lesions may all be presenting symptoms of a leukemic process. The greatest difficulty, however, usually lies in the fairly large group of cases characterized by refractory anemia, associated with leukopenia and thrombopenia. This triad of hematological signs ("pancytopenia") should immediately suggest bone-marrow involvement by a leukemic process. It is in these cases that the bone-marrow biopsy is of great diagnostic value.

**Treatment**—In the field of treatment, the use of *radio-active phosphorus* is being watched with interest. Lawrence, Scott and Tuttle<sup>76</sup> report careful metabolic and clinical studies with "labelled"

phosphorus in 6 patients with leukemia. With large doses, decreases in the number of leukocytes similar to those following x-radiation can be produced. Striking therapeutic results were not obtained. In a more recent paper Warren<sup>77</sup> reported on the results of treatment in 4 "acute" cases. In 2 of these, a definite remission was obtained. As Warren points out, there is really no point in giving the material to chronic cases, since x-radiation is just as valuable and probably better controlled. However, in the acute types, any experimental method is justifiable. The therapeutic results in Warren's cases seem promising, although there is great question in the Reviewer's mind whether the 2 cases with remission were actually acute.

**Leukocytic Neoplasms**—The best known neoplasms of white cells are lymphosarcoma and Hodgkin's disease. An extensive and valuable review of 196 cases of *lymphosarcoma* is given by Sugarbaker and Craver.<sup>78</sup> The tumor usually begins and runs its early course only in lymph-nodes, although in one-third of the cases it started in the tonsils and nasopharynx and occasionally in the gastrointestinal tract. Treatment with **x-radiation** resulted in a 5-year survival rate of 15.9 per cent. For clinically early cases in a *local area*, **radical surgical removal** is worthy of consideration (the same is true of Hodgkin's disease). The use of divided doses in single doses of 400 to 600 roentgens with total dosage per field of 2000-3000 roentgens yielded the best results.

Interest in a possible etiology of *Hodgkin's disease* has recently been revived by the group at Duke University who believe that the organism of brucellosis may be of etiological significance. Histological studies of the lymph-nodes of a case of apparently typical brucellosis

with positive blood culture, etc., revealed the characteristic findings of Hodgkin's disease. Further studies of typical cases have revealed a high percentage of positive growths of the brucella organism in lymph-nodes. Because of the many previous organisms, which have been found in association with the disease, these reports must be received with a certain skepticism, although there can be no question that this is highly important work which should be actively pursued.

Closely resembling Hodgkin's disease in some cases is *Boeck's sarcoidosis*, a condition which is receiving increasingly greater attention. There may be localized or generalized adenopathy, mediastinal adenopathy, pulmonary involvement, splenomegaly, and involvement of bones. Skin lesions were first discriminated, but may not be present in some cases. Peculiar lesions of the eyes (iridocyclitis and keratitis) may be present. Histologically, the lesions resemble somewhat those of tuberculosis, peculiar giant-cells being common. Harrel<sup>79</sup> reports 11 carefully studied cases. Etiologic studies, with emphasis on fungi and acid-fast bacilli, were entirely negative. Intradermal tests with pathologic material were also negative. There is usually leukopenia, neutropenia and monocytosis, with an increased sedimentation rate. The serum protein (globulin) values are often increased and substances resembling Bence-Jones protein were occasionally found in the urine. No specific treatment was discovered. The possibility that the condition may be an exaggerated nonspecific response to a lipid fraction of varied organisms is present. The Reviewer has seen several cases. One responded well to **x-radiation** given to lymph-node groups and skin; 2 have responded well to x-ray therapy given over the medias-

tinal and pulmonary masses; and 1 responded to *splenectomy* performed for thrombocytopenic purpura. The condition should be seriously considered in any adenopathy or splenomegaly, particularly if there is mediastinal or pulmonary involvement and skin lesions are present.

Another condition simulating Hodgkin's disease at times, and at others chronic lymphatic leukemia, is *giant follicle lymphoma* or *follicular lymphoblastoma*. Articles on this subject are contributed by Baggenstoss and Heck,<sup>80</sup> and Baehr and Klemperer.<sup>81</sup> This disorder is relatively benign, very radio-sensitive, and may last for many years. The onset is insidious, with general or regional adenopathy and splenomegaly, anemia is at first absent and usually no abnormal cells are found in the blood. The average duration of life in the cases observed by Baggenstoss and Heck was 4½ years, but 2 patients have lived for 17 years. Histologically, there is extreme enlargement of the lymphoid follicles in lymph-nodes, spleen, and other lymphoid structures, resembling superficially certain toxic or inflammatory conditions of lymph-nodes. In some cases the differential diagnosis from infection is very difficult.

An important article from the diagnostic and prognostic standpoints is that of Woodward and Craver regarding the serum phosphatase in the "*lymphomatoid*" diseases. These authors state that a complete roentgenographic study of cases of *Hodgkin's disease* at various stages would probably reveal perhaps as much as a 50 per cent incidence of gross bone changes. The question of bone lesions is important in relation to the treatment of Hodgkin's disease, lymphosarcoma, and the leukemias. It was thought, therefore, that a clue to bone involvement could be

given by the serum phosphatase. The alkaline phosphatase was frequently elevated in Hodgkin's disease, less often in lymphosarcoma and the leukemias. The elevation in phosphatase often antedated positive roentgenographic findings in patients who complained of bone pain. A persistently elevated serum phosphatase in cases of Hodgkin's disease probably indicates invasion of bone. The elevation of phosphatase is probably a measure of the defense mechanism of the bone against invasion by the Hodgkin's process.

Another interesting neoplasm of lymphoid cells is "*multiple myeloma*" which is in reality plasmacytoma—a tumor composed of abnormal lymphocytes called plasma-cells. Interesting articles regarding this condition are those of Haden and Rumsey,<sup>82</sup> and Ulrich.<sup>83</sup> Haden points out that the presenting symptom was usually pain, almost always in the back, chest, or abdomen, and that physical examination was not significant. The commonest roentgen finding was demineralization of the spine, often with collapse or compression of vertebrae. Changes in the ribs and skull were common. Sternal puncture was done in 16 cases and plasma-cell hyperplasia was found in 9 instances. Anemia was present in most cases. The sedimentation rate was often elevated and excessive rouleaux formation (due to high plasma globulin) was usually present. Bence-Jones proteinuria, high serum proteins, and renal involvement are all discussed. Response to irradiation unfortunately is very poor. In Ulrich's more comprehensive article, the following further points are brought out: Multiple myeloma is a neoplastic disease occupying a position between frank tumors and diffuse (leukemic) hyperplasia; the cells, although they resemble plasma-cells, are really of myeloid origin; extramedullary origin of

the tumor may occur; renal disease is a common complication.

### Hemorrhagic Diseases

**Hemophilia**—Work on the nature of hemophilia continues to be pursued at the Thorndike Laboratory (Boston). It was previously shown that the clot-promoting power of normal plasma was present in the globulin fraction of the plasma, from which an extract containing "globulin substance" could be prepared by acid precipitation. Further work has demonstrated, however, that normal plasma contains more regularly effective clot-promoting materials which are associated with plasma euglobulin. From these it is hoped that further fractionation will result in the development of an extract effective in the treatment of hemophilia. At present, the only definitely effective treatment is a *transfusion* of either whole blood or plasma.

Brinkhous<sup>84</sup> presents a somewhat different idea regarding the *pathogenesis* of hemophilia. Studies made by this observer demonstrated that in hemophilic blood the prothrombin was converted to thrombin unusually slowly. This delay in prothrombin conversion could be corrected by adding less than 1 mg. of crude thromboplastin to 100 cc. of the abnormal blood. Brinkhous believes that the beneficial effects of transfusion are due to the addition of thromboplastin, derived from cells and platelets. The experiments of Quick<sup>85</sup> lead to the same conclusions.

Aggeler and Lucia<sup>86</sup> perform a valuable service in investigating the potency of a large number (17 in all) of so-called blood coagulating substances. They found that the claims for coagulative potency of these preparations was, to say the least, greatly exaggerated. Most of them were completely inactive. Only those substances suitable for local use

(like certain snake venoms) were at all active. Similar studies are reported by McGavack<sup>87</sup>. In the light of these investigations, the alleged effects of *oxalic acid* intravenously in the treatment of hemophilia must be greatly discounted. A report on the use of this chemical is that of Page, Russel, and Rosenthal,<sup>88</sup> who claim a good effect in 3 cases of hemophilia by the use of repeated intravenous injections of 5 to 10 mg. The actual case reports, however, are quite unconvincing, and it is reassuring that the conclusion is made that "its use, along with other known beneficial measures, *notably multiple transfusions* (italics ours), would be warranted in attempting to control bleeding in hemophilia."

McGavack<sup>87</sup> also reports on the use of a substance similar to oxalic acid in the treatment of hemophilia. This is an extract derived from shepherd's purse and containing dicarboxylic acids. In 4 cases of hemophilia treated with this material ("*koagmin*") there was prompt shortening of the coagulation time, lasting for 2 to 4 hours.

An excellent article on certain *effects of hemophilia on the growing skeleton* is contributed by Caffey and Schlesinger.<sup>89</sup> Simple hemarthrosis, panarthrititis, subperiosteal hemorrhage are all carefully considered. An interesting hemorrhagic diathesis with prolonged coagulation time, associated with a circulating anticoagulant, is reported by Lozner, Jolliffe, and Taylor.<sup>90</sup> The case differed from hemophilia not only clinically but in certain physiological respects: A transfusion failed to shorten the clotting time; normal human plasma and "globulin substance" were ineffective *in vitro*. There was, furthermore, the striking finding in the blood of a substance interfering with the completion of the normal clotting mechanism.



The patient's plasma, when added to normal blood, prevented clotting.

**Purpura—Thrombocytopenic Purpura**—The pathology of the bone-marrow in idiopathic thrombocytopenic purpura has been studied by Limarzi and Schleicher.<sup>91</sup> Uniform findings were marked hyperplasia (increase) of megakaryocytes with a shift to young forms. In the chronic form, the megakaryocytic hyperplasia exceeded that of the acute cases. Speculation is made regarding the possibility that the spleen in this disease may have an unusual inhibitory effect on platelet production by the bone-marrow megakaryocytes. This is confirmed by some recent (unpublished) work of E. B. Miller and the Reviewer. Despite the almost complete absence of platelets from the circulating blood in the idiopathic type of thrombopenic purpura, the bone-marrow is crowded with megakaryocytes. These, however, produce few if any platelets. Directly following splenectomy there is a striking increase in megakaryocytic activity with the production of large numbers of platelets, reflected in the peripheral blood by a rapid increase in the platelet count.

Wiseman, Doan, and Wilson<sup>92</sup> state, however, that "sternal marrow studies have consistently revealed normal numbers of normal appearing megakaryocytes in a normal cellular setting." They also state they are convinced (from their supravital studies) that there is increased activity of splenic clasmotocytes in destruction of platelets. In other words, they maintain that the marrow is normal, but the spleen is destroying an increased number of platelets in the disease. These findings are directly contrary to those of the Reviewer and of other workers who have carefully studied the megakaryocytes in the marrow.

As diagnostic essentials of idiopathic thrombocytopenic purpura, Wiseman and

his associates list the following: Spontaneous purpura with or without free bleeding from mucous membranes; definite decrease in blood-platelets, normal coagulation and prothrombin times, no unusual anemia or leukocytosis, absence of pathologic cells in both the blood and the marrow, absence of recent history of the ingestion of drugs, no appreciable enlargement of spleen or lymph-nodes.

Regarding therapeutic measures, x-radiation over the spleen is considered worthless; the use of snake venom "has not been encouraging"; parathyroid extract was tried without favorable result. Transfusions help to tide a patient over either until a spontaneous remission becomes established or splenectomy is done. It is gratifying to note that "full doses" of blood are recommended, in contradistinction to the enconiums of various authors to use "small" transfusions. Why the "small" transfusions should possess any special virtue is a mystery which the Reviewer has never been able to fathom. Thus, medical measures are usually worthless, although they may help as a stop-gap measure. **Splenectomy** is the only real cure. In the chronic case, the decision for splenectomy must be made after repeated observations of the patient's course. The acute cases "demand energetic action" and this is summarized as follows: Confirmation of diagnosis by **sternal puncture**; immediate **transfusions**; if blood loss persists, **splenectomy** is not postponed. Of 9 splenectomized cases, 1 died of postoperative shock and the others made uneventful recoveries. It has been the Reviewer's experience in several cases that too much temporizing and indecision regarding splenectomy have led to cerebral hemorrhage and death. In the acute case, the "bull must be taken by the horn" and splenectomy quickly performed before

the patient has had a chance to bleed into vital tissues.

Thrombocytopenic purpura in relation to the *menarche* is discussed by Goldburgh and Gouley.<sup>93</sup> Pubertal menorrhagia may be the first indication of purpura. **Splenectomy** is curative and is indicated when repeated *transfusions* of blood and *endocrine therapy* have failed to check the hemorrhagic tendency.

Purpura hemorrhagica due to ingestion of *sedormid* is again reported in an article by Falconer and Schumacher.<sup>94</sup> This drug occasionally causes typical thrombocytopenic purpura, apparently as a sensitization phenomenon (*cf.*, amidopyrine and agranulocytosis). Another drug occasionally resulting in thrombocytopenic purpura is *arsphenamine*, which is also reported upon by Falconer with Epstein.<sup>95</sup> Careful studies demonstrated an allergic sensitivity of certain patients to the drug, the sensitivity expressing itself solely upon the platelets.

**Other Types of Purpura**—1. *Non-thrombocytopenic* — Purpura occurs either when the blood-platelets become extremely low or when there is damage to the capillary wall. These cases are usually differentiated as follows:

	THROMBOCYTOPENIC PURPURA (Low platelets)	VASCULAR PURPURA (Normal platelets, capillary abnormality)
Platelet count	Low	Normal
Clotting time	Normal	Normal
Bleeding time	Increased	Usually normal, but may be increased
Clot retraction	Poor	Normal
Tourniquet test	Positive	Positive

Most cases of purpura fall into these 2 groups. There are rare cases, however, in which, although the platelet count is normal, the platelets themselves are abnormal. These cases may be familial; because of the platelet abnormality, clot retraction is poor and bleeding time is pro-

longed. Other familial cases of purpura are probably exaggerated forms of vascular purpura, in which the bleeding time is prolonged although the platelet count, platelet morphology, and clot retraction are all normal. Brunn,<sup>96</sup> in reporting a large family of bleeders, prefers the designation of *hereditary hemorrhagic diathesis* for these cases which have been termed "pseudohemophilia" by v. Willebrand and others. In Brunn's cases, a hemorrhagic tendency present in both sexes had been present in 4 generations and in 15 of 23 members. Four cases had bled to death. The outstanding abnormality was a greatly prolonged bleeding time (over an hour) with normal platelets and a normal platelet count, the tourniquet test being either normal or slightly positive.

A quite benign familial abnormality is described by Davis<sup>97</sup> under the name of "*hereditary familial purpura simplex*." Spontaneous ecchymoses, mostly in women, were the presenting symptom. Diligent examination of the families demonstrated numerous other cases. No hematological abnormalities were found, the only finding being a positive capillary resistance test in 16 of 25 cases tested.

One family also showed hereditary telangiectasiae (Osler-Rendu-Weber disease). Rheumatoid arthritis and rheumatic fever were common in the families studied.

For topical application in cases of vascular purpura and perhaps in other

hemorrhagic conditions, including hemophilia, in which the bleeding point can be visualized, the use of *Russel viper venom (stypven)* has been studied and recommended by Page and Thomas.<sup>98</sup> Pledgets soaked in the solution are applied directly to the bleeding point; all intervening clots or other obstructions must be cleared away. Packing is sometimes advantageous. The venom may also be dropped directly onto the hemorrhagic area from the point of a small-caliber hypodermic needle. Sprays of venom from an atomizer may be used in the nasopharynx or to control bleeding from the uterine cervix. The Russel viper venom appears to accelerate the action of thromboplastic substances and to act with the latter in a synergistic manner.

2. *Hypoprothrombinemia—Vitamin K Deficiency* — The recognition, careful study, and treatment of hypoprothrombinemia—vitamin K deficiency—represent one of the milestones of medical progress of the past decade. The story of vitamin K, its deficiency, its value in clinical medicine is by now well-known. For the interested reader, the review by Quick<sup>85</sup> is recommended. A hemorrhagic disease of chicks fed on a deficient diet was found to be due to a deficiency in a fat-soluble vitamin, which was called vitamin K (*koagulation*). Vitamin K deficiency in chicks was found to be associated with an increase in the prothrombin coagulation time, and it was soon discovered that the hemorrhagic tendency in cases of obstructive jaundice was also due to an increased prothrombin time. The test which has proved of greatest value in determining the prothrombin time is that of Quick.<sup>99</sup> An important advance in performance of the test is the preparation of a stable thromboplastin, as described by Souter, Kark and Taylor.<sup>100</sup> This is a lyophilized rabbit brain extract which can be kept indefinitely. It is suspended

in salt solution before use. The greater the prothrombin time, the lower is the concentration of prothrombin in the blood. At a percentage concentration of prothrombin of less than 60, spontaneous bleeding may occur, or the patient may bleed continuously from incised wounds. The concentration of prothrombin in the blood was found to be directly correlated with vitamin K intake or absorption. In obstructive jaundice, vitamin K is not absorbed or manufactured and hypoprothrombinemia develops. Vitamin K by mouth or parenterally in these cases results in an increased prothrombin concentration of the blood, a decrease in prothrombin clotting time, and in cessation of bleeding tendency.

Vitamin K deficiency develops in other conditions than obstructive jaundice, *i. e.*, inadequate dietary, particularly of fats; impaired gastrointestinal digestion; unusual loss of fats from the bowel, and severe hepatic damage. Prolonged dietary deficiency as a cause of hypoprothrombinemia is emphasized by Kark and Lozner.<sup>101</sup> In the 4 cases studied, multiple deficiencies were present (scurvy, subclinical pellagra), thus offering further evidence that nutritional deficiency in man is rarely, if ever, confined to a single factor. In the newborn infant, a potential hypoprothrombinemia is probably usually present, and in some infants, a hemorrhagic tendency may develop with excessively low prothrombin values. Quick and Grossman<sup>102</sup> found that the prothrombin concentration of infants' blood, nearly normal at birth, drops abruptly during the first few days of life, and then usually recovers rapidly. This is thought to be due to the establishment of a bacterial flora in the intestines, thus initiating the synthesis of vitamin K which becomes available to the organism for the production of prothrombin. The cause of hemorrhagic disease of the newborn is

due to a delayed restoration of the prothrombin level. The condition may be very severe but is promptly cured by the oral administration of vitamin K. Similar conclusions have been arrived at by Dam, Tage-Hansen and Plum,<sup>103</sup> and by Owen, Hoffman, Ziffren and Smith.<sup>104</sup> A monograph on *hypoprothrombinemia neonatorum* is that of Salomonsen<sup>105</sup> based on 66 cases.

Shettles, Delfs and Hellman<sup>106</sup> make the important observation that the plasma prothrombin level of the newborn infant can be raised not only by feeding **vitamin K concentrate** directly to the infant after birth, but also by administering it to the mother prior to delivery. The values obtained in the infant by maternal administration are often 3 times those normally seen, and in general are higher than those which can be attained by administering vitamin K concentrate to the baby after birth. The Squibb vitamin K concentrate was used.

Poncher and Kato<sup>107</sup> emphasize a micro-method for the determination of prothrombin in infants and report on the treatment of 22 infants with hemorrhagic disease (hypoprothrombinemia) of the newborn. The average prothrombin time of 10 patients before treatment was 210 seconds (normal about 25 seconds) and in 12 other patients was more than 300 seconds. Synthetic preparations of **vitamin K** were administered either orally, intramuscularly or subcutaneously. A demonstrable effect to treatment was present within 2 to 6 hours. Transfusions were not necessary.

The most important cause of hypoprothrombinemia is *obstructive jaundice* in which, due to a lack of bile in the intestines, the fat-soluble vitamin K is not properly absorbed. The first therapeutic triumphs with vitamin K were obtained in the often dangerous hemorrhagic tendency occurring in such cases. The tend-

ency to hypoprothrombinemia is probably enhanced by concomitant hepatic damage and an inadequate intake of foods containing vitamin K. Stewart and Rourke<sup>108</sup> discuss the control of the prothrombin deficiency in obstructive jaundice. The more prolonged the obstruction and the greater the liver damage, the more marked is the prothrombin deficiency. Operation itself reduces prothrombin, probably due to such factors as blood loss, effect of anesthetic, and cessation of intake of vitamin K. In *treatment*, the authors advise not only **vitamin K** but measures to improve liver function, *i.e.*, **carbohydrates, fluids, and early decompression of the obstructed biliary tract.**

The *treatment* of vitamin K deficiency is becoming much simpler with the elaboration of numerous synthetic products some of which may be given parenterally. Analysis of the chemical structure of vitamin K and its synthesis represent a great chemical triumph. As Kark and Souter<sup>109</sup> bring out, it was only 4 years after the discovery of vitamin K by Dam in 1935 that Doisy and his associates demonstrated conclusively that vitamin K<sup>1</sup>, the active principle in alfalfa, was represented by the formula 2-methyl, 3-phytyl, 1-4 naphthoquinone, thus confirming the tentative suggestions published simultaneously by 4 groups of investigators, including Fieser. The most active product was found to be 2-methyl, 1, 4-naphthoquinone; this was relatively stable and could be readily manufactured. Kark and Souter report on the treatment of 18 patients with hypoprothrombinemia by the parenteral administration of a water-soluble derivative of **2-methyl, 1, 4-naphthoquinone**. Within a few hours of the intravenous or intramuscular administration of the material the bleeding was satisfactorily controlled and the prothrombin time was normal. On the other

hand, 12 patients with hypoprothrombinemia associated with hepatic disease did not respond to intensive parenteral administration. Thus, if the prothrombin time of a patient with jaundice fails to become normal after treatment, it is evident that hepatic disease is present and the prognosis poor. Frank, Hurwitz and Seligman<sup>110</sup> report on the intravenous administration of an oily suspension of the original vitamin K<sub>1</sub> (2-methyl, 3-phytyl, 1-4 naphthoquinone). A single intravenous administration of 10 mg. suspended in 1000 cc. of salt solution resulted in a return to a normal prothrombin level within several hours, and maintenance of this level for *several days*. A simpler means of administering the vitamin is that of intramuscular administration, as pointed out by Andrus and Lord.<sup>111</sup> The material used was 2-methyl, 1, 4-naphthoquinone dissolved in corn oil, each cubic centimeter containing 1 mg. of the drug. Single injections intramuscularly of as little as 2 mg. restored the plasma prothrombin level by as much as 48 per cent, an effect becoming evident within 8 hours after injection. The effect of a single injection might be prolonged for as long as a week, during which no toxic effects were noted.

### Spleen Disease

Very little that is new has been reported during the past year on this subject. The pathogenesis of so-called *Banti's disease* is discussed by Thompson<sup>112</sup> on the basis of 137 well-studied cases falling into the general category.

It was found that the condition resulted from a variety of primary lesions that produce splenic vein hypertension. The conclusion is made that the syndrome is a secondary mechanical congestive splenomegaly and that there is no reason for assuming the presence of an unknown toxic agent or for retaining the concept of

3 stages in the development of Banti's disease. Cirrhosis of the liver exists only as 1 of several obstructive mechanisms (it was present in 68 per cent of the cases); if it is not present at the time of splenectomy, *it will not develop subsequently*. The splenic histology is the same in all types. Extrahepatic lesions responsible for *congestive splenomegaly*, which is suggested as a better term than Banti's disease, are thrombosis of portal or splenic veins, compression of the splenic vein by tumor or other causes, congenital stenosis of the portal vein (infants and children), etc.

The *removal of very large spleens* is discussed by Henry.<sup>113</sup> This author has had considerable experience in removing the large spleens so commonly found in the tropics. It is emphasized that splenectomy in these cases frequently results in a relaxation of the diaphragm caused by "loss of the cushion on which it has long been moulded and stretched." It is well-known that chest complications are frequent following splenectomy and, in order to obviate these effects, Henry recommends the use of a rubber balloon attached to a source of CO<sub>2</sub> and left in place under the diaphragm in the splenic bed after removal of the spleen. The balloon may be gradually deflated and removed after a few days.

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## METABOLISM

*Edited by* HENRY J. JOHN, M.D.

## CARBOHYDRATE METABOLISM

*By* C. N. H. LONG, M.D., Sc.D.

Understanding of carbohydrate metabolism has been widely extended in the last 5 years and a very considerable amount of literature, particularly concerning the regulatory action of the endocrine glands, has appeared during this period. The following review articles contain extensive discussion of certain of the more important phases of this subject: Long,

Katzin and Fry,<sup>1</sup> Young,<sup>2</sup> Himsworth,<sup>3</sup> Soskin,<sup>4</sup> Cori,<sup>5</sup> Russell,<sup>6</sup> Szent-Györgyi.<sup>7</sup>

The concept of all phases of metabolism as a steady state rather than an equilibrium has been advanced, particularly by the brilliant studies of Schoenheimer and his colleagues<sup>8</sup> in which the transformations of various foodstuffs are followed by incorporating into their molecules the

isotopes of hydrogen and nitrogen. This work is unfolding a picture of cellular activity in which all the cellular components, not excluding the proteins, are continually undergoing exchange with the metabolites brought to them by the circulating fluids. The ensuing turnover of the cellular substances proceeds at a remarkably rapid rate so that even the so-called "inert" fat depots are in the rat half removed and half replenished in a period of a week. Not only may whole molecules be so exchanged but even certain of their constituent groups. Thus, by the operation of a specific enzyme the amino group of the alpha-amino-acids may be transferred to the carbon residues (alpha-keto-acids) resulting from the deamination of other amino-acids or in the course of carbohydrate metabolism and thus new amino-acids formed. This process known as "*transamination*" has been extensively studied by Braunstein and Kritzman<sup>9</sup> and by Cohen.<sup>10</sup>

Furthermore, it is now realized that common intermediates may be derived from all the major foodstuffs, such a one is pyruvic acid ( $\text{CH}_3\text{-CO-COOH}$ ), a substance whose importance in intermediary metabolism is certain to increase as investigation proceeds. Thus, at a certain stage of the metabolism of all the foodstuffs the identity of carbohydrate, protein and perhaps fatty acids becomes merged and it may well be that the actual cellular requirements for energy and growth are met by a much smaller number of intermediary metabolites than was once supposed.

Finally, it has been shown that even the end-product of carbon oxidation, *i. e.*,  $\text{CO}_2$ , may itself participate in synthetic reactions leading to the formation of such substances as urea, oxaloacetic acid and even liver glycogen. The participation of the water derived from the oxidation of the hydrogen of the foodstuffs in synthetic

reactions has, of course, been known for some time.

While the extraordinary rapidity and complexity of the cellular processes presents a picture difficult of comprehension, it must be remembered that it is by virtue of these continuing processes, which constitute a steady state, that the cell remains alive. Once equilibria are established, the cell no longer displays the characteristics of living material and it is only by the continual expenditure of energy that these characteristics, such as selective permeability, increase in size, cell division, etc., are maintained.

The 2 subjects, therefore, that have aroused the most intense interest in recent years are (*a*) the enzyme systems of cells and the mechanisms of the reactions they catalyze and (*b*) the factors regulating the activity of cells. In the following discussion of carbohydrate metabolism these topics will be the ones most emphasized, since they are those in which the most significant advances may be said to have occurred.

### Absorption of Carbohydrates

The *intestinal absorption* of the physiologically important carbohydrates, glucose, fructose and galactose, is not governed by the simple laws of diffusion since all 3 pass through the intestinal wall several times faster than the smaller pentoses. The mechanism of this selective absorption has excited a good deal of discussion and a clear understanding of it is still lacking.

Considerable interest has been aroused by the claim of Verzár and his colleagues that certain agents and procedures reduce this selective absorption by virtue of their effect on phosphorylation processes in the intestinal wall. The agents used were phloridzin and iodoacetic acid substances which are claimed to inhibit phosphorylation in kidney and muscle re-



spectively. In addition, adrenalectomy was also claimed to reduce the intestinal absorption of glucose and this was further interpreted by Verzár to indicate that the adrenal cortical hormone was concerned with phosphorylation. These experiments have not been universally confirmed but the considerable importance of phosphorylation in other stages of the intermediary metabolism of carbohydrate suggests that the processes involved in the transfer of glucose across the intestinal wall are of a similar character.

The recent work of Althausen<sup>11</sup> points to the participation of the *thyroid* in the absorption of glucose. He has shown that after thyroidectomy in rats the rate of absorption is much decreased and, conversely, that the administration of thyroxin to normal rats increases the rate. These findings have had an interesting sequel, for Russell<sup>12</sup> has found that the decreased rate of glucose absorption in hypophysectomized rats is due to the concurrent thyroid atrophy and could be corrected by the injection of thyroxin. This hormone, although it also increases the depressed basal metabolic rate of these animals, does not restore the other defects in their carbohydrate metabolism.

The participation of certain *endocrine glands* in the mechanisms governing glucose absorption from the intestine has a practical application when glucose is given by mouth to test the assimilating capacity of the organism for this substance. A "flat" type of curve may indicate no more than a disturbance of the absorptive ability of the intestine while a "high" type of curve may result from the same cause. Thus, it seems probable that the flat curves observed in hypopituitarism and hypothyroidism are in part at least due to this, as is the high curve sometimes observed in hyperthyroidism. In such cases it is best to test the toler-

ance by the intravenous injection of glucose.

### Liver and Regulation of Blood Glucose

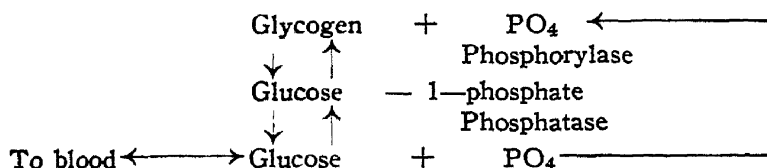
The essential rôle of the liver in intermediary metabolism continues to be emphasized. It is now recognized that this organ is the sole source of the blood glucose and is the organ in which the transformation of noncarbohydrate material into glucose (and glycogen) occurs.

In a series of papers Soskin and his colleagues<sup>4</sup> have emphasized the active participation of the liver in the regulation of the blood glucose. While exception can be taken to their claim that the liver is the site of glucose formation from fatty acids, nevertheless, their evidence for the existence of "homeostatic" mechanisms regulating the supply of glucose to the tissues by the organ is convincing and important. Under normal conditions and with an intact endocrine system, the liver meets the demands of the organism by increasing or decreasing its output of glucose. Thus, after a meal containing carbohydrate the liver reduces its supply of glucose and at the same time deposits some of the ingested material as liver glycogen while during fasting it supplies a quantity of glucose sufficient to maintain the blood glucose level and satisfy the needs of tissues such as those of the nervous system which apparently only use this substance for their needs.

Upon these metabolic processes certain endocrine organs act as a regulatory mechanism. Insulin is stated to depress glucose formation from noncarbohydrate sources while the hormones of the adrenal cortex and anterior pituitary increase glucose formation from these sources.

The extensive studies beginning with the work of Claude Bernard on the formation of liver glycogen have been climaxed in the past 2 years by the work

of Cori and his collaborators<sup>5</sup> on the intermediary steps involved in liver glycogen formation and breakdown. Until recently there was a widespread belief that these transformations were effected by the activity of a liver "amylase." This has been shown not to be the case, but, instead, the first step in the hydrolysis of the liver glycogen is a phosphorylation, catalyzed by a specific enzyme (phosphorylase). This leads to the formation of glucose 1-phosphate, which is then attacked by a second enzyme (a phosphatase) which liberates free glucose and regenerates the phosphate ion which then re-enters the reaction.



By separating the 2 enzyme systems and allowing the phosphorylase to act upon glucose 1-phosphate in suitable concentrations, glycogen synthesis *in vitro* was achieved, a most notable contribution. Similar mechanisms have since been shown to exist in yeast; Kiessling<sup>13</sup> and in plants.<sup>14</sup> The universality of phosphate transfer in carbohydrate breakdown in living cells of all types is of great interest.

It may be presumed, although not yet fully demonstrated *in vivo*, that the synthesis of glycogen is accomplished by the preliminary phosphorylation of glucose to form glucose 1-phosphate which is then polymerized to glycogen and the phosphate freed. The way would now seem clear for an investigation of the effects of such well-known glycogenolytic agents as epinephrine on these isolated systems.

The influence of various hormones on the liver glycogen continues to receive attention. The question as to whether insulin *directly* affects glycogen formation from noncarbohydrate sources is still un-

settled. Bach and Holmes put forward evidence from liver slice studies that this hormone inhibited the deamination of amino-acids, a preliminary step in the formation of glucose from protein. On the other hand, Stadie and his colleagues,<sup>15</sup> who have extensively investigated this question by the same technic, found that such an effect was limited to the so-called unnatural or dextrorotatory compounds and could not find any influence of this hormone on the natural or levorotating forms. If their results are correct then this action of insulin is somewhat of a curiosity since only very small amounts, if any, of the dextrorotatory

acids are present in the foodstuffs. However, since the liver and kidney contain a d-amino oxidase that only attacks the unnatural forms, premature conclusions should not be drawn as to the significance of the observations of Stadie.

It has now been established by several observers that the adrenal cortical hormones substantially increase the liver glycogen of fasting animals apparently at the expense of the tissue proteins (Long, Fry and Katzin<sup>1</sup>; Britton and Silvette).

The action of anterior pituitary extracts is not yet clearly defined, probably on account of the impurity of these preparations which contain a number of hormones that either directly or indirectly influence carbohydrate metabolism. Thus, depending on the conditions of the experiments, an increase, decrease or no change in the liver glycogen has been reported to follow their injection.

The precursors of the liver glycogen are now known to be definitely the physiological sugars, glucose, fructose and galac-

tose, certain amino-acids, glycerol and such carbohydrate intermediaries as pyruvic and lactic acid. The formation of glucose (and glycogen) from the even numbered fatty acids is still the subject of a lively controversy. For a statement of the opposing views the recent papers of Soskin<sup>4</sup> and Stadie<sup>16</sup> should be consulted. However, the very recent papers of Stadie would seem to show very clearly that in the diabetic liver this transformation does not occur and, since it is the diabetic state that this change was supposed to be proceeding at a maximal rate, it is quite unlikely that it is a normal pathway of metabolism of any major consequence.

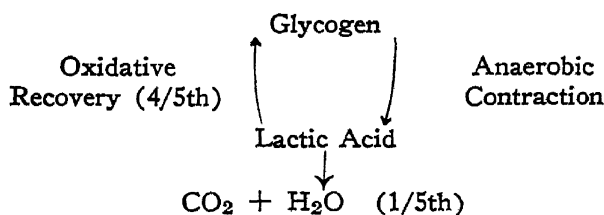
### Intermediary Carbohydrate Metabolism of Muscles

Practically all knowledge of carbohydrate utilization and oxidation in the tissues has been derived from the study of skeletal muscles. This is not only because these tissues constitute nearly half the body weight and, hence, are the seat of the major part of metabolism, but because muscular movements that place such a heavy demand on the energy supply of the body are carried out to a large degree by the breakdown and utilization of the muscle carbohydrates. Nor is it probable that the mechanisms involved in these phases of metabolism are unique to the skeletal muscles. Indeed, there is every reason to believe that carbohydrate utilization is carried out in all tissues by the same systems and for that matter even in such lowly organisms as yeast.

The appearance of lactic acid in muscles in rigor mortis had been observed for many years but that it had its source in

muscle glycogen was not known until the work of Parnas and Wagner in 1914. Prior to this, in a classical paper, Fletcher and Hopkins had shown that lactic acid appeared in a stimulated muscle and disappeared again during recovery. They also made the important observation that much greater quantities of lactic acid appeared under anaerobic conditions and was not removed until oxygen was available. Since muscle will contract for considerable periods without oxygen the association of these phenomena was evident but its real significance was not appreciated until the work of Meyerhof, whose first paper appeared in 1920. In this paper Meyerhof showed that there was a relationship between the oxygen consumption, glycogen disappearance and lactic acid formation of exercised frogs' muscles.

The figures showed that lactic acid appearance during stimulation of isolated frogs' muscles was equivalent to glycogen disappearance and that the oxygen consumption which took place during recovery only accounted for a part (one-fifth) of the lactic acid that disappeared during this period. The remaining quantity of lactic acid that was removed was accounted for by the resynthesis of glycogen. As a result of these experiments, together with the measurements of heat production during contraction and recovery by A. V. Hill, it was thought that these reactions accounted for the energy production of muscle and that the carbohydrate cycle that occurred formed the basis of muscular contraction. The events taking place during activity then could be represented as follows:



This simple scheme has, however, not entirely stood the test of further investigation although there is no doubt that muscle glycogen forms on breakdown not glucose, as does the liver glycogen, but passes through a variety of other intermediates of which lactic acid is the one that accumulates in greatest quantity when the oxygen supply is deficient.

Even prior to the work of Meyerhof it was appreciated that glycogen did not form lactic acid directly. Embden, in an extensive series of papers between 1914 and 1927, had shown that hexose phosphates, particularly glucose 6-phosphate, were formed in contracting muscle and that these substances then gave rise to lactic acid. At this point the analogy between carbohydrate breakdown in muscle and yeast became particularly striking.

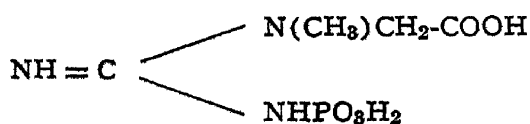
Harden and Young had found in 1908 that the fermentation of glucose by yeast involved a preliminary phosphorylation and that alcohol and  $\text{CO}_2$  production paralleled the formation of this ester. Furthermore, they showed that ester formation was catalyzed by a yeast enzyme—hexokinase. In muscle, lactic acid and  $\text{CO}_2$  are the end-products but, as Meyerhof showed, the yeast enzyme will also catalyze glucose breakdown in muscle extracts. Finally, it was shown that the muscle extracts contained not 1 enzyme but a whole series of catalysts that degrade glycogen in a stepwise manner.

The dissection of this chain of events has occupied the attention of a large number of investigators in recent years, and while the whole cycle is not yet complete, enough is known to indicate that the general pattern of carbohydrate breakdown

both in muscle and yeast is almost identical.

Before discussing this it is necessary to mention another investigation that clearly indicated the simple mechanism of Meyerhof and Hill was unsatisfactory as a full explanation of the chemical processes occurring in contracting muscle. In 1930, Lundsgaard had found that if animals (rabbits or frogs) were injected with iodoacetic acid ( $\text{CH}_2\text{I}-\text{COOH}$ ) and the muscles were stimulated, they contracted for a while and then went into rigor. Examination of the muscles showed that although glycogen had decreased, no lactic acid formation had occurred. Instead, considerable quantities of hexose phosphates had accumulated. Even more significant were the alterations in the creatine phosphate content of the tissue, for this substance was decomposed to an even greater extent than in the untreated muscles. This indicated that the first reaction occurring in contraction was not the breakdown of glycogen to lactic acid but was preceded by that of creatine phosphate. It was also evident that iodoacetic acid blocked the chain of reactions involved in glycogen breakdown at some point between hexose phosphate and lactic acid. This work, while it did not invalidate that of Hill and Meyerhof, clearly showed that the chemical processes concerned with muscular contraction were more complicated than their original theory suggested.

The presence of creatine phosphate in muscles had been discovered 3 years previously both by Eggleton and Eggleton and Fiske and Subbarow. Its formula is:



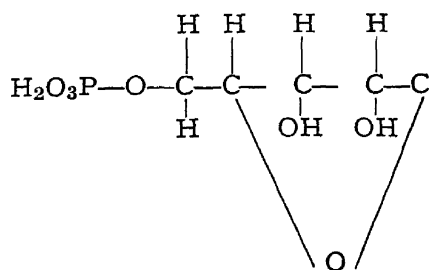
*Creatine Phosphate*

These investigators had found that during muscular contraction this substance is split into creatine and phosphoric acid which renders phosphate available for combination with the muscle carbohydrate.

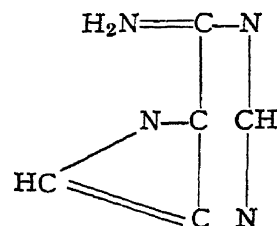
Furthermore, during recovery creatine phosphate is resynthesized. Thus, not

only is there a carbohydrate cycle in muscle but also one involving phosphate.

Creatine phosphate, however, is not the only phosphorus compound that undergoes decomposition during muscular contraction. Embden and Zimmerman, in 1927, had isolated adenylic acid from muscle. Its formula is:



*Adenylic Acid*

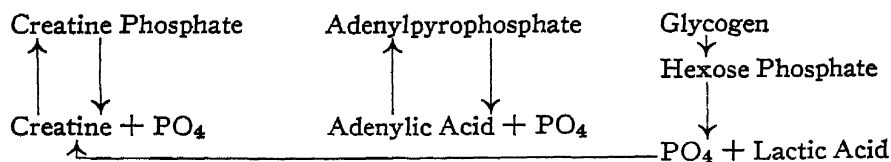


This substance is a mononucleotide and contains in addition to the phosphate radical, a pentose, *d*-ribose, and a purine, adenine.

Two years later, Lohmann isolated from muscle the pyrophosphate of this compound known as adenylic acid pyrophosphate or adenylypyrophosphate. This substance is a key compound in the processes involved in carbohydrate breakdown in muscle. It acts as a co-enzyme and during muscular contraction is broken down to adenylic acid, yielding 2 mole-

cules of phosphate which then phosphorylates the carbohydrate.

The relation of creatine phosphate to these changes is that the former apparently acts as a phosphate reserve from which adenylypyrophosphate is regenerated. A partial reconstitution of creatine phosphate under anaerobic conditions is made possible by the fact that the phosphate attached to the carbohydrate in the initial stages is later discarded and hence made reavailable for further carbohydrate decomposition.

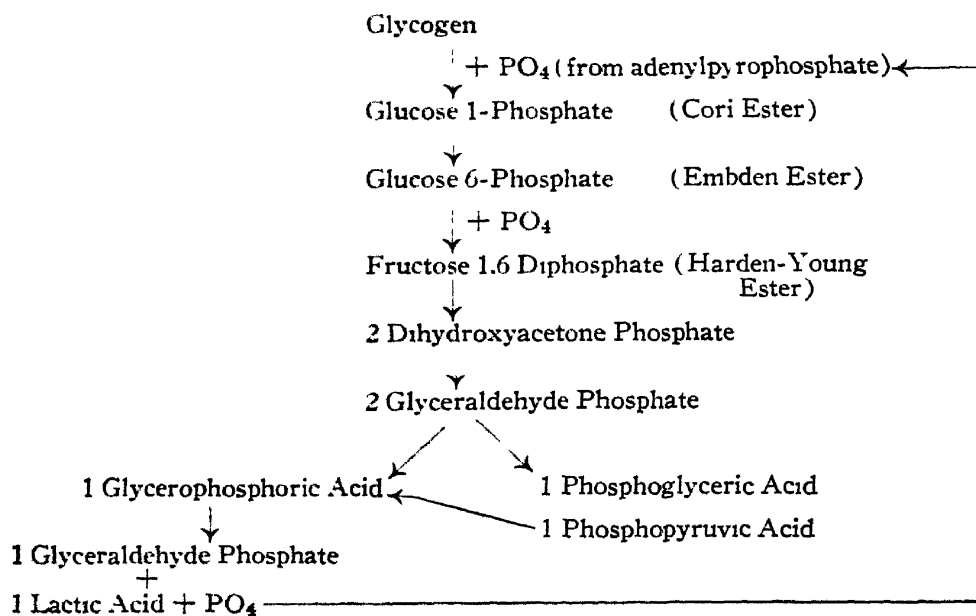


These changes, it will be observed, are all anaerobic and involve the transfer of phosphate first to the carbohydrate and then back again to the adenylypyrophosphate *via* creatine phosphate.

Further study has shown that between the initial formation of hexose phosphate

and lactic acid several other intermediaries are involved.

The present conception of the chain reactions occurring appears on the following page, but is subject to further modification as this active phase of investigation is pursued.



It will be observed that the initial stages of glycogen breakdown on muscle are similar to those in liver, since glucose 1-phosphate is formed in both tissues. However, in liver this is immediately decomposed to glucose and phosphate. In muscle the addition of a second phosphate radical together with a reorientation of the carbohydrate molecule yields fructose diphosphate whose metabolic pathway is then fixed so that lactic acid is in muscle the end-product of glycogen breakdown.

There are still 2 important questions to be considered. The first of these is the manner in which the glycogen stores of muscle are replenished. It will be recalled that the original Meyerhof scheme (largely worked out on isolated frog muscles) postulated that four-fifths of the lactic acid formed was reconverted into glycogen, the oxidation of the remainder providing the necessary energy. However, in the intact mammal with its rapid circulation considerable quantities of the lactic acid formed during hard muscular exercise may escape into the blood stream and consequently become unavailable for such a process. Even

more damaging, however, is the fact that lactic acid, while a good precursor of liver glycogen, apparently does not form muscle glycogen when infused into an animal (Long and Horsfall). Furthermore, as Long and Grant showed in fasted rats during recovery from exercise, lactic acid removal from both the muscles and blood is comparatively rapid while muscle glycogen regeneration is slow but if glucose is given its regeneration soon occurs (C. N. H. Long and E. G. Fry—unpublished results). Consequently, in the *intact* animal muscle glycogen regeneration is largely dependent on the glucose brought to it by the blood stream and it is also entirely possible that the lactic acid that accumulates in muscles when the oxygen supply is deficient is largely removed by the blood and converted by the liver into glucose before it can serve again as a source of muscle glycogen.

The second question is of even greater importance. The conversion of glycogen to lactic acid yields only a small part of the energy of the glycogen available for work and is consequently a most uneconomical method for its utilization. Oxida-

tion, on the other hand, yields all the available energy. It is certain that glycogen can be degraded to lactic acid under anaerobic conditions in muscle but it is not at all certain that this is the usual pathway except under conditions in which the oxygen supply is inadequate to meet the rate of work, *i. e.*, severe exercise. In any case, the lactic acid formed must ultimately be oxidized and the question has been raised as to whether carbohydrate oxidation can occur in muscle without an intermediary formation of lactic acid by anaerobic processes.

A clear distinction should be drawn between the anaerobic and aerobic degradation of carbohydrate. The former may well be an emergency mechanism allowing muscular activity to take place and repaying the oxygen at a later date during recovery—the oxygen debt. From the extensive studies of Hill, Long and Lupton it is known that all except the mildest forms of exercise are associated with an increased blood lactic acid and a period of extra oxygen consumption after the exercise is finished. Evidently, some metabolites accumulate, particularly at high levels of work, that require oxidation before the organism returns to its pre-exercise condition. The dissociation of work from the necessity of a contemporary oxygen supply of sufficient magnitude is a distinct advantage, since short violent efforts can be made at a level of energy expenditure far beyond that available to the muscles through their blood supply. Thus, a man can run 100 yards in somewhat under 10 seconds without drawing a breath, yet following this, his tissues will consume in the next hour an extra 10 liters of oxygen. Since the maximum oxygen supply that can be transported by the blood is around 5 liters a minute, the advantage in being able to accumulate a large oxygen debt

is apparent and not only from the point of view of athletic performances alone.

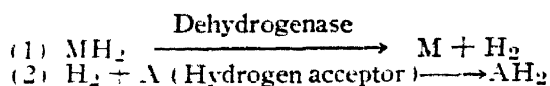
The mechanisms by which glycogen or lactic acid or other metabolites are oxidized in muscles have also been extensively studied in recent years. The oxidation of metabolites by tissues, although essentially consisting of the union of oxygen with their carbon, hydrogen, nitrogen or sulfur atoms, is carried out by the operation of a complicated series of enzymes and catalysts, whose action is co-ordinated so that the degradation of the molecules proceeds in a step-like manner. Since only a certain proportion of the total energy of the metabolite is liberated by each step, a smooth delivery of this energy is afforded in a manner most advantageous to the cell. The rapid oxidation by cells of substances that outside the body are regarded as unusually stable compounds is a remarkable demonstration of the efficiency of these biological systems.

In order to understand the present knowledge of the oxidation of the carbohydrates and their derivatives, it is first necessary to describe these enzyme systems in general terms.

In the first place, the oxidation of an organic compound can take place (*a*) by the direct addition of oxygen to it or (*b*) by the withdrawal of hydrogen. A moment's thought will show that dehydrogenation leaves the molecule in a more highly oxidized and more unstable condition and, furthermore, can occur in the absence of oxygen provided that some other compound is available to which the liberated hydrogen can be attached. Such a compound is termed "*a hydrogen acceptor.*" The hydrogen of the metabolite is loosened from its attachment in the parent molecule by the action of an enzyme known as a "*dehydrogenase.*" These are specific in their nature and are usually named after the substrate upon

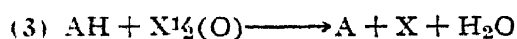
which they act, i. e., lactic acid dehydrogenase.

The interaction between metabolite, dehydrogenase, and hydrogen acceptor may be featured as follows:



Now, in order for this system to work continuously, it must be reversible, which means that the reduced hydrogen acceptor must be oxidized and thus returned to its original state.

This is carried out by the interaction between the reduced hydrogen acceptor and an oxidizing enzyme (oxidase).

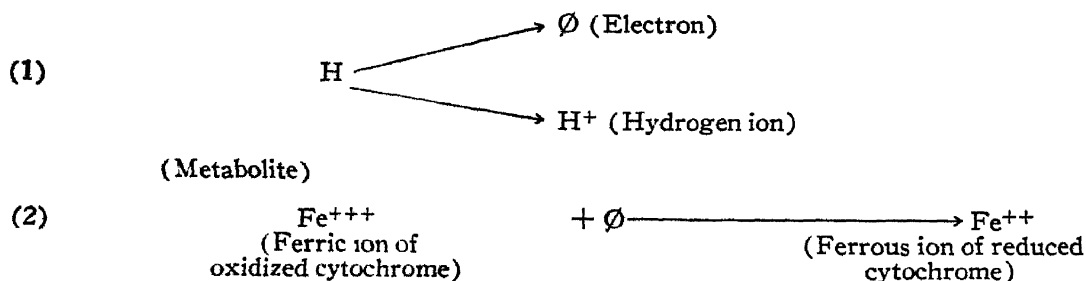


The now reduced oxidase is reoxidized by oxygen brought to the cell by the blood and the process starts over again. Summing this equation shows that, as a result of the operation of this series of enzyme, there has occurred an oxidation of the hydrogen of the metabolite to water. The union of hydrogen with oxy-

gen yields the maximum quantity of energy. This union, however, has not occurred immediately but over a series of steps at each one of which part of the energy of the hydrogen is released.

As to the actual enzymes involved there exists, as indicated above, a series of dehydrogenases which activate the hydrogen of the metabolite so that it can unite with the hydrogen acceptor. The most important hydrogen acceptors in muscle are the cytochromes, iron-containing pigments related to haem and which, like this respiratory pigment, are combined with a protein. Three such substances have been recognized in muscle and are termed *cytochrome A, B and C*. All participate in cellular respiration and probably act in series.

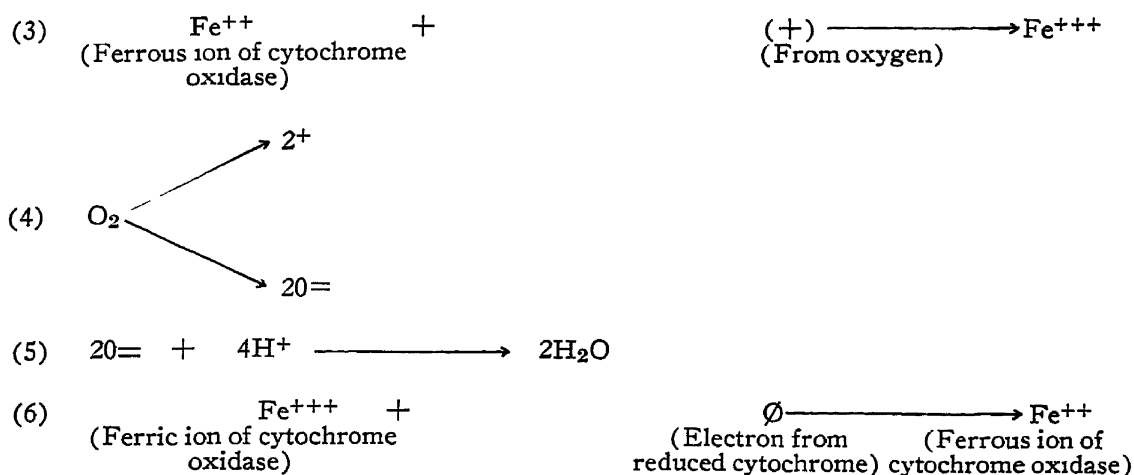
The oxidation and reduction of the cytochromes consists in the alternate oxidation and reduction of the iron atom they contain, so that what actually occurs when the cytochrome accepts hydrogen from the substrate is the acceptance by the iron atom of an electron donated by the hydrogen.



The further union of the hydrogen ion with oxygen and the re-acceptance of the electron from reduced cytochrome is affected by another enzyme termed "*cytochrome oxidase*." This enzyme is also known by the name of "*Warburg's respiratory enzyme*" (*Atmungsferment*). It also contains iron atoms in organic combination (probably a haem) which are united to a specific protein.

The oxygen carried to the cell unites with the cytochrome oxidase and oxidizes its iron atom which, in turn, accepts the electron from the cytochrome. The oxygen having donated a positive charge to the ferrous atom becomes an oxygen ion. Two such ions will then unite with 4 hydrogen ions derived from the metabolite and form 2 molecules of water.

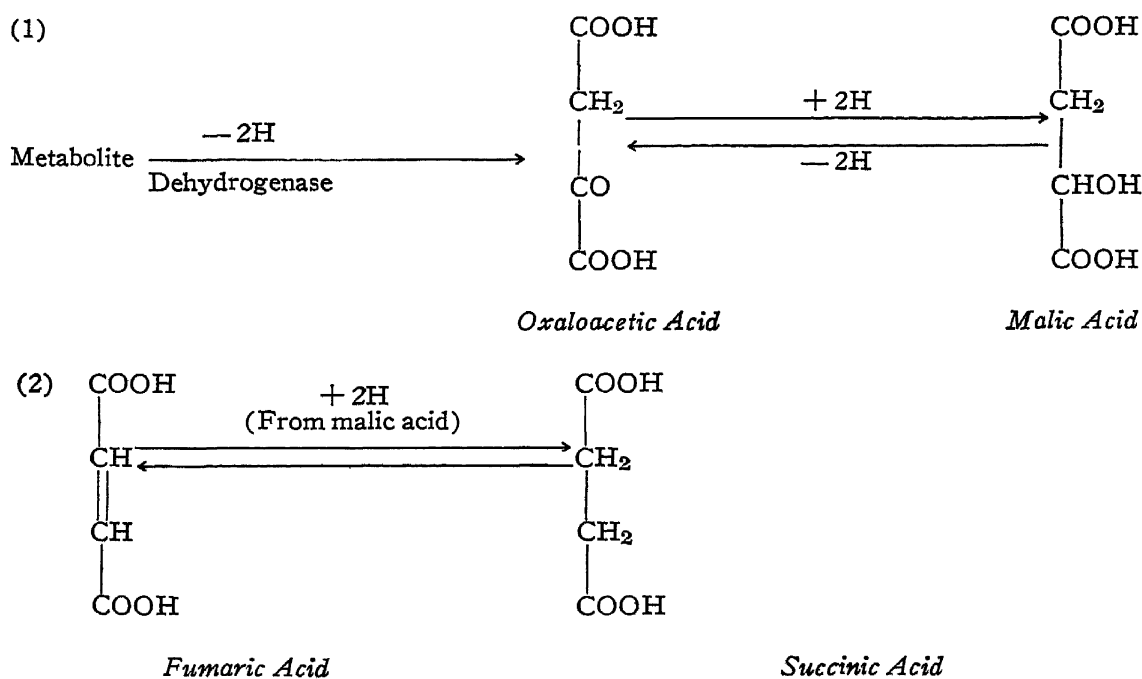


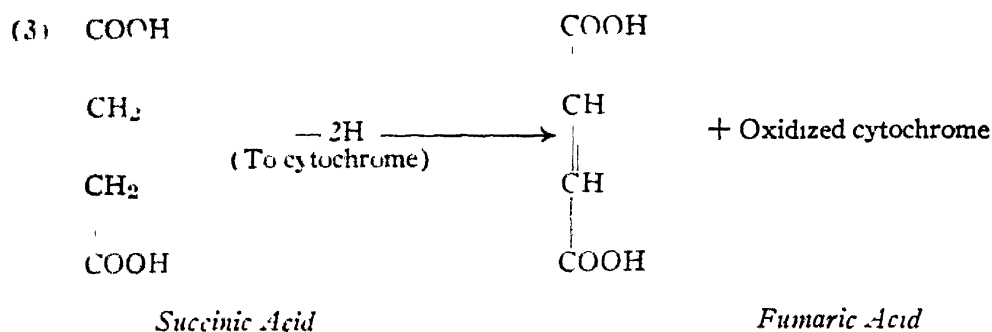


It should be noted that the rôle of oxygen is limited to the acceptance of an electron derived from hydrogen and the union of the ensuing oxygen ion with the hydrogen ions to form water. The transfer of hydrogen, however, involved further enzymes and catalysts than those indicated above. It has been shown by Szent-Györgyi<sup>7</sup> that between the dehydrogenases and the cytochromes is inserted a series of catalysts that heretofore had been regarded merely as metabolites.

These are the dicarboxylic acids, oxaloacetic, malic, fumaric and succinic acids. The discovery of their catalytic action in cellular respiration is based on the observation by Szent-Györgyi that the addition of minute traces of fumaric acid to minced and washed pigeon-breast muscle would support the respiration which soon declined in its absence.

Further extensive investigation showed that these dicarboxylic acids acted as follows:





Two pairs of dicarboxylic acids are involved. In the first stage (1) the hydrogen of the metabolite reduces oxaloacetic acid to malic acid. This then yields by the action of a dehydrogenase 2 atoms of hydrogen to fumaric acid (2), thus regenerating oxaloacetic acid and reducing the fumaric acid to succinic acid. The action of another dehydrogenase (succinic acid dehydrogenase) then allows the passage of 2 hydrogen atoms to cytochrome (3) which then carries the hydrogen forward as already described while at the same time reducing the succinic acid back to fumaric acid.

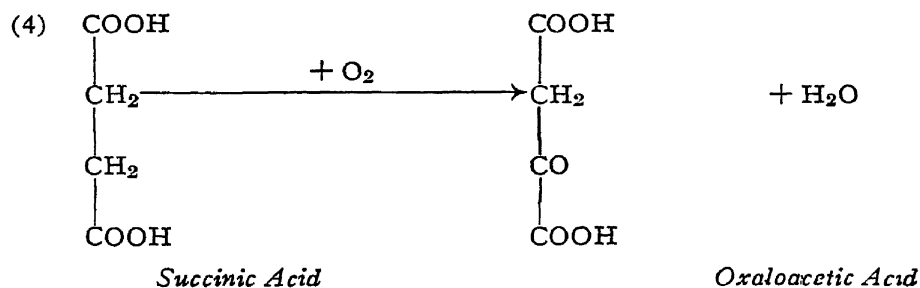
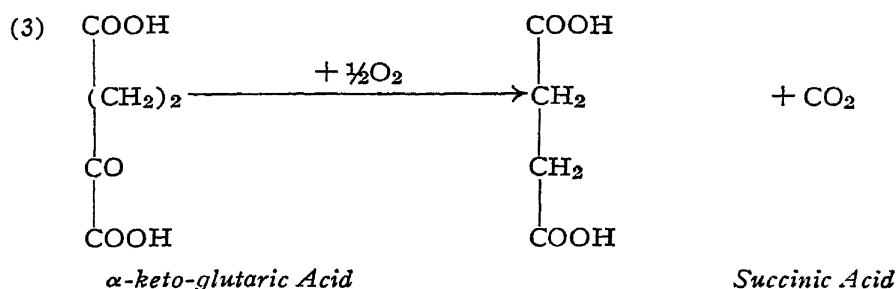
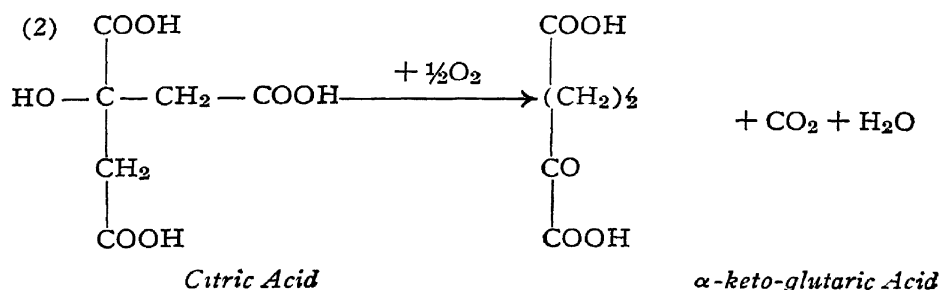
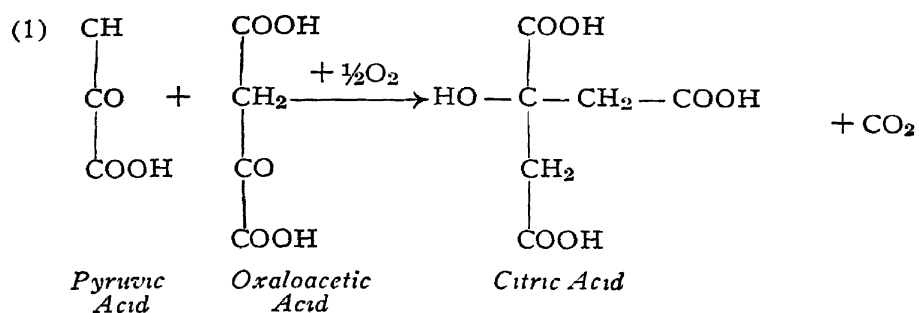
The hydrogen of the metabolite is thus passed steadily over these 2 pairs of dicarboxylic acid, liberating at each step a certain portion of its energy.

One of the questions most frequently asked is the *source of the CO<sub>2</sub> that appears during respiration*, since the above scheme only postulates the oxidation of hydrogen to water. This problem has not yet been successfully solved, but 2 views have been put forward. Szent-Györgyi believes that the respiratory CO<sub>2</sub> arises by processes independent of the oxidation of hydrogen. He postulates that at some stage following the dehy-

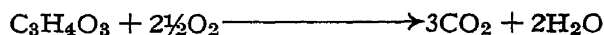
drogenation of the carbohydrate molecule pyruvic acid is formed which is then decarboxylated yielding CO<sub>2</sub>. Pyruvic acid is a highly reactive substance that can react both under aerobic and anaerobic conditions with a variety of substances. Thus, by direct decarboxylation, such as occurs in yeast, it yields CO<sub>2</sub> and alcohol. In brain it may follow several pathways all of which, however, yield CO<sub>2</sub>, or it may be both oxidized and decarboxylated to yield CO<sub>2</sub> and acetic acid.

It is of exceeding interest that the co-enzyme of the decarboxylating system is the diphosphate of vitamin B<sub>1</sub> (Lohmann and Schuster).

Krebs and Johnson have put forward a scheme that not only accounts for the oxidation of hydrogen but for that of carbon as well. This is, in a sense, an extension of Szent-Györgyi's work but involves the addition of other steps, particularly the formation of citric acid by the union of oxaloacetic and pyruvic acid. It is claimed that citric acid, like fumaric and succinic acids, catalyzes the respiration of washed pigeon muscle, a point on which all investigators are not agreed.<sup>17</sup> In brief, the "citric acid cycle" is:



It will be observed that the net result of these reactions is the oxidation of 1 molecule of pyruvic acid to  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , viz.:



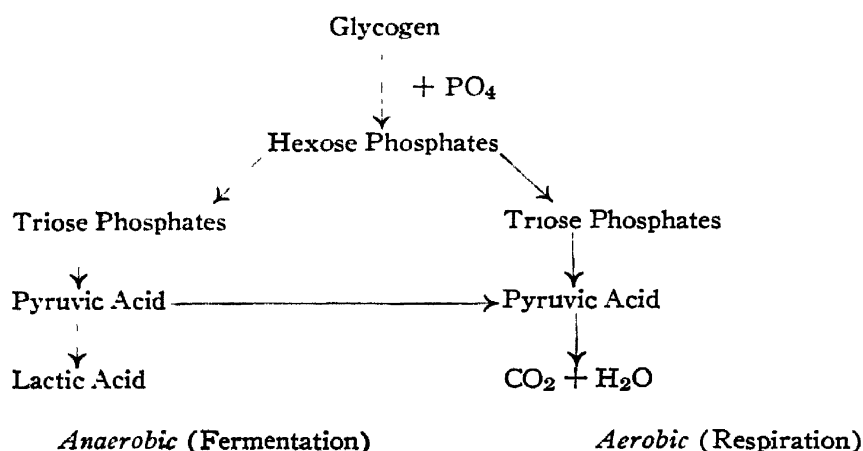
The original molecule of oxaloacetic acid has been regenerated and is able to start the chain of reactions again by combining with another molecule of pyruvic acid (or another triose).

In a recent paper, Colowick, Kalckar and Cori<sup>18</sup> have shown that in cell-free extracts of heart-muscle and kidney the phosphorylation of glucose is coupled with the succinic-fumaric oxidative sys-

tem and that the oxidation of 1 molecule of glucose is accompanied by the phosphorylation of 5 molecules of glucose. Since the oxidation of glucose follows the path of triose phosphate—phosphoglycerate—pyruvate— $\text{CO}_2 + \text{H}_2\text{O}$ , these substances are apparently common intermediates in both the aerobic and anaerobic breakdown of glucose. In the absence of oxygen, pyruvic acid is

transformed into lactic acid. These authors point out that while in these cell-free systems the oxidative energy is used to phosphorylate glucose in the intact cell, this energy can be utilized for a variety of other cellular activities.

It is now possible to incorporate in a condensed scheme what is known concerning the anaerobic and aerobic breakdown of carbohydrate in muscle.



It should be emphasized that all the foregoing schemes are necessarily incomplete and in some cases are no more than approximations to the actual conditions existing in intact cells.

The muscles are not limited to the utilization of carbohydrates for their energy supply. It is known that they oxidize the acetone bodies with equal facility and can probably utilize amino-acids and fatty acids as well. Consequently, it must be assumed that they possess equally efficient enzyme systems for these metabolites. Of these not a great deal is known at present. Glutamic acid dehydrogenase is present in muscle and by its action converts the amino-acid into  $\alpha$ -ketoglutaric acid, an intermediary in the Krebs' "citric acid cycle." Such a change suggests that many intermediary metabolites may be derived from all the major foodstuffs

and hence may ultimately follow a common path. A conspicuous example of these is pyruvic acid which is derived both from carbohydrates and protein (by the oxidative deamination of alanine). By condensation with acetic acid, beta-hydroxybutyric acid, a fatty acid intermediary, may also be found (Krebs and Johnson).

For an extensive discussion of biological oxidation the reader is referred to Szent-Györgyi's book<sup>7</sup> or the recent monograph by Green.<sup>19</sup>

In summary it may be said that carbohydrate utilization in muscles receiving an adequate oxygen supply may be entirely oxidative and not involve lactic acid formation. On the other hand, it seems clear that under circumstances where the oxygen supply is deficient, lactic acid is formed by anaerobic processes and is then oxidized when oxygen

becomes available. A third possibility is that the initial stages of carbohydrate breakdown are always anaerobic, since the rapidity with which the oxygen requirement rises during muscular activity is far beyond the immediate capacity of the oxygen transporting mechanism. At a later date this may become adequate and the contraction process entirely oxidative, a view that is taken by Sacks.<sup>20</sup> Obviously, however, in severe exercise for short periods the energy requirements must be met by anaerobic breakdown or metabolites which are oxidized or otherwise removed after the effort.

The primary reaction in muscular contraction is unknown but it seems likely that 1 of the keys is adenylypyrophosphate, whose decomposition initiates the glycolytic cycle and is also responsible for the preliminary phosphorylation of muscle glycogen, which may then follow either the aerobic or anaerobic path of metabolism.

### **Carbohydrate Metabolism of Heart**

The heart is the most important muscle in the body and operates under somewhat different circumstances from either voluntary or involuntary muscle. The cardiac muscle is in continuous activity and has not the advantage of the other muscles in being able to rest for comparatively long periods. Consequently, it is not surprising to find that the cardiac muscle is exceedingly dependent on a contemporary supply of oxygen and only possesses a limited ability to go into oxygen debt (Katz and Long) and to accumulate lactic acid. Nevertheless, the heart contains considerable quantities of glycogen which is apparently utilized and rebuilt in the same manner as in skeletal muscle. If an adequate oxygen supply is available, the carbohydrate content changes but little over a long period; but a reduction or complete

withdrawal of the oxygen supply leads to rapid glycogen disappearance, although the beat ceases long before this has proceeded to the point reached in skeletal muscle (G. T. Evans). A prolongation of activity may be obtained in isolated hearts if they are perfused with fluids rich in glucose so it may be presumed that under anaerobic conditions glycogen breakdown forms a major source of energy. Cardiac muscle also contains phosphocreatine and adenylypyrophosphate and it is probable that these play a similar rôle to that in voluntary muscle.

Under aerobic conditions the heart is in no way dependent on carbohydrate alone for its energy requirements and can also, like voluntary muscle, oxidize protein and fat as well. According to Evans,<sup>21</sup> the heart will also oxidize lactate directly and this may furnish nearly half the energy requirements under normal circumstances. Furthermore, it also can use beta-hydroxybutyric acid.<sup>22</sup>

The relation of an altered cardiac metabolism to disease is an important question but so far no important correlations have been made. It is known, however, that diphtheria toxin decreases the cardiac glycogen and that infarction of the heart muscle is followed by a reduction in both glycogen and phosphocreatine.

For a more detailed discussion of cardiac metabolism the reader is referred to the book by Clark<sup>23</sup> and the review by Evans.<sup>21</sup>

### **Carbohydrate Metabolism of Nervous System**

The nervous tissue is unique in that its sole source of energy appears to be glucose or such related substances as lactate, pyruvate or succinate. This dependence is clearly shown by the behavior of brain slices in a respiration apparatus. Unless 1 of the above sub-

stances is added to the Ringer solution in which the slices are suspended, the respiration soon fails, but if these are present, it is maintained for long periods (Himwich and Nahum). Himwich and Nahum studied the metabolism of the brain *in situ* and found that, regardless of the quantity of carbohydrate that was being oxidized in the remainder of the body, the brain always oxidized carbohydrate. This was true even in totally depancreatized animals. The implications of these studies are exceedingly interesting. In the first place, the nerve-cells seem to require only 2 substances, oxygen and glucose, for their metabolic needs. Reduction of the latter by such measures as insulin provokes serious disturbances in the nervous system, culminating in convulsions and death. Reduction of the oxygen supply, as is well known, also excites a violent response. Now, while limitation of the oxygen supply is ultimately fatal to all tissues, reduction of the glucose supply is without effect on any tissue except that of the nervous system. Thus, Himwich and Fazekas have shown that as the blood glucose is decreased by insulin, the oxygen consumption of the brain declines along with its glucose utilization, but the muscles of the same animal, while also showing a comparable reduction in carbohydrate utilization, do not diminish their oxygen consumption indicating, as has been pointed out before, that this tissue is able to draw on substances besides glucose for its energy requirements.

In recent years insulin and metrazol have been widely used in the treatment of various forms of nervous diseases of a functional nature. As Himwich, Bowman, Fazekas and Crenstein have pointed out, insulin depresses cerebral metabolism by withdrawing glucose, while

metrazol exerts its effect by decreasing the oxygen supply.

### Endocrine Control of Carbohydrate Metabolism

Until a few years ago the only endocrine glands known to influence carbohydrate metabolism were the islands of Langerhans and the adrenal medulla. Since then, however, knowledge has been greatly extended by the proof that the anterior pituitary and the adrenal cortex are also of major importance; while of even greater significance is the emergence of the concept that the regulatory activity of the endocrine system is an integrated one in which the anterior pituitary is the dominant member.

Nevertheless, a great deal of confusion still prevails in this field so that the exact action of even such a well-defined hormone as insulin is still a matter of dispute.

1. **Anterior Pituitary**—This endocrine gland is unique, inasmuch as it not only secretes hormones that act directly on the tissues, *i. e.*, the growth and lactogenic hormones, but also controls the activity of the thyroid, adrenal cortex and gonads by means of specific substances termed "tropic hormones." Consequently, the analysis of the effects of hypophysectomy or crude anterior pituitary extracts upon carbohydrate metabolism is a complicated one as any student of this subject will soon find by a perusal of the current literature. This analysis is also rendered difficult by the multiple activity of the anterior pituitary and by the often overlooked fact that any agent that depresses carbohydrate utilization must, in a secondary manner, increase fat catabolism. Therefore, anterior pituitary extracts may not only excite an increased secretion of other hormones that influence metabolism, but may also produce alterations in the metabolism of all the

major foodstuffs. It is particularly the latter that has suggested to some investigators that the anterior pituitary contains a very large number of metabolic hormones. Indeed, some conclude that there are separate "growth" and "protein metabolism" hormones as well as separate "ketogenic," "fat metabolism," "diabetogenic" and "carbohydrate metabolism" hormones. It may be expected that this confusion will be resolved as soon as the chemical purification of the anterior pituitary principles is more advanced than it is at present. The question may be left here and a summary of the well-authenticated effects of this gland upon carbohydrate metabolism outlined.

(a) Hypophysectomized animals rapidly deplete the carbohydrate levels of the muscles, liver and circulation fluids when fasted for relatively short periods so that fatal hypoglycemia occurs. The depletion of the glycogen content of the muscles is particularly striking, since intact animals maintain these for very long periods without food. Furthermore, normal animals maintain their blood glucose by the conversion of protein and, consequently, it may be assumed that the removal of the hypophysis not only reduces this but also, as Russell has shown, leads to an excessive rate of glucose utilization. The combined result of both these effects must be a rapid lowering of the blood glucose.

The injection of crude anterior pituitary extracts into fasting hypophysectomized animals not only prevents the hypoglycemia but also conserves the muscle glycogen.

(b) When hypophysectomized animals are fed a known amount of glucose and the manner in which they dispose of it is compared with that of normal animals, it will be found that the former deposit less of the glucose as liver and muscle glycogen and oxidize a larger proportion.

This, again, indicates the excessive rate of glucose oxidation that occurs when the inhibiting effect of the anterior pituitary is removed.

This inhibiting action is further emphasized by the results of the injection of anterior pituitary extract into normal rats fed glucose. It has been found<sup>6</sup> that under these circumstances the oxidation of glucose is greatly depressed and much larger quantities of the fed glucose are deposited as muscle glycogen.

These results are in harmony with the earlier and exceedingly important experiments of Houssay and his colleagues. These investigators found that not only did the respiratory quotient of normal dogs injected with anterior pituitary extract fail to rise after glucose feeding but that the continued daily injection of such extracts resulted in profuse glycosuria and acetonuria. This effect they termed "diabetogenic," and this discovery must be ranked as one of the most important since the observation of Minkowski that removal of the pancreas produced the same result. Taken in conjunction with the demonstration, also by the Houssay school, that hypophysectomy produces a striking amelioration of a total pancreatic diabetes, they constitute an eloquent illustration that not only is a normal carbohydrate metabolism dependent upon the interaction of at least 2 endocrine glands (the pancreas and anterior pituitary), but also that the same metabolic disturbance (glycosuria) may be produced either by the excision of the one or the hyperactivity of the other.

These studies were climaxed by the remarkable work of Young<sup>2</sup> who has shown in dogs that if the anterior pituitary injections are given in sufficient quantity for a long enough period that the glycosuria did not disappear on their cessation, as it did in Houssay's experiments, but continued for an indefinite

period. In other words, a permanent diabetes was produced by exposure of the animal to a brief but intense hyperpituitarism. The continuance of the diabetic state has been shown to be due to the degeneration and destruction of the islands of Langerhans that is brought about by the anterior pituitary extract. Thus, a diabetes that began as a consequence of hyperpituitarism was continued by the secondary involvement of the insulin-secreting cells of the pancreas. The implications of these findings in understanding the etiological factors in human diabetes is both obvious and important.

It may be concluded that the anterior pituitary hormones inhibit carbohydrate utilization. This not only leads to an elevated blood glucose and accumulation of muscle glycogen but, as a secondary effect, diverts the metabolism to that of fat. In consequence, acetonuria, lipemia and an accumulation of fat in the liver are to be expected and, indeed, have been repeatedly demonstrated.

(c) Another observation of the Housay school is that removal of the hypophysis greatly increases the sensitivity of these animals to the hypoglycemic action of insulin. Furthermore, this action can be completely abolished in normal animals that have previously been injected with anterior pituitary extract. These effects are undoubtedly related to those described above since it has been pointed out that the removal of the hypophysis alone will precipitate hypoglycemia and when such a powerful hypoglycemic agent as insulin is added, the fall in the blood glucose becomes precipitous. Furthermore, normal animals probably in part recover from insulin hypoglycemia by their ability to mobilize glucose from noncarbohydrate sources and this also is defective when the anterior pituitary is removed.

The obliteration of the action of insulin in injected normal animals would seem to be due to the antagonistic action between this hormone and that of the anterior pituitary, since the former increases the rate of glucose removal from the blood while the latter inhibits its utilization by the tissues. The exact effect on the blood glucose of a mixture of the two will depend on the relative proportion of each hormone in it, so that much larger quantities of insulin will be required to bring about a certain depression of the blood glucose than are necessary in untreated animals. This phenomenon of insulin resistance is occasionally encountered in human diabetics and not infrequently in individuals suffering from acromegaly in whom, of course, glycosuria or an impaired carbohydrate tolerance is a common finding.

2 **Pancreas**—The exact method by which insulin influences carbohydrate metabolism is not yet understood. This hormone increases the rate of glucose removal from the blood, increases the muscle glycogen if sufficient carbohydrate is supplied and in fed animals, with the exception of the young rabbit, decreases the liver glycogen. When the extra glucose deposited as muscle glycogen is balanced against the reduction in blood glucose, and liver glycogen and the amount of glucose given, it is found that a considerable quantity is still unaccounted for. Since the respiratory quotient increases, the great majority of investigators believe that the hormone has increased the rate of glucose oxidation in the tissues (very largely in the muscles). The view that insulin is primarily concerned with some phase of glucose oxidation is in harmony with the effects of pancreatectomy, where it is assumed that the primary defect is an inability to oxidize glucose at a sufficiently rapid rate to supply the needs of the tissues.



To this theory of diabetic metabolism and the action of insulin Soskin<sup>4</sup> has taken exception. Since he vigorously supports the view that the primary defect in diabetic animals is an unrestricted formation of new glucose in the liver both from protein and fatty acids, he regards insulin as an inhibiting agent of these processes and, since the urinary glucose-nitrogen ratio (2 or 3 to 1) is not compatible with an impaired ability to oxidize glucose, he states that insulin does not influence glucose oxidation in the tissues. From his experiments he concludes that at the high blood glucose levels prevailing in depancreatized animals, the rate of oxidation is the same as in normal animals at their lower blood glucose level. In a recent extensive review he states that insulin catalyzes muscle glycogen formation from glucose but does not accelerate its oxidation.

The truth of this hypothesis rests on 2 premises (*a*) that fatty acids are converted into glucose in the liver; (*b*) that the peripheral oxidation of glucose is not impaired in depancreatized animals. The former has been debated for a number of years but the recent work of Stadie<sup>16</sup> would indicate that it does not occur. If this is so, it becomes exceedingly difficult to retain the second premise, since the source of the large quantity of glucose required to account for the glycosuria plus a normal oxidation of it in the tissues cannot be protein and there is no evidence of any other substance, except fatty acids, that are present in sufficient quantity.

Nevertheless, even if it is assumed that insulin does not accelerate glucose oxidation, the exact point in its intermediary metabolism at which this influence is exerted is still problematical. The recent developments in knowledge of the enzyme systems involved, together with a clearer understanding of the reactions

by which glucose is transformed into  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , offers the possibility that in the near future the point at which insulin is necessary may be found. Krebs has already reported experiments from which he deduces that insulin participates as a catalyst in the citric acid cycle (*cf.* above), but since this effect appears to be limited to bird muscle, its significance is somewhat limited.

Recently, Haist, Campbell and Best<sup>24</sup> have reported their findings on the influence of various conditions on the insulin content of the pancreas. They find that a high carbohydrate diet increases the content, while fasting, fat feeding, or the injection of anterior pituitary extract bring about a depletion. The results with anterior pituitary extract are exceedingly interesting, since, as has already been pointed out, the continued injection of such an extract is able to cause a permanent diabetes associated with destruction of the islands of Langerhans.

**3. Adrenal Cortex**—A direct participation of the adrenal cortex in the hormonal control of carbohydrate metabolism has been the subject of vigorous debate for a number of years. The interest in this problem has centered not only in the interpretation of the alterations in carbohydrate metabolism that occurs in adrenalectomized animals, but also on their relation to the function of the adrenal cortex. This problem would appear to be capable of a simple solution were it not for the fact that other changes follow adrenalectomy that at first sight appear to be of greater significance than the disturbances in carbohydrate metabolism.

The most important of these other changes are the widespread disturbances in water and electrolyte balance and, in consequence, several groups of investigators have concluded that the chief func-

tion of the adrenal cortex is the control of these phases of metabolism and that any alterations in carbohydrate metabolism are of a secondary character.

On the other hand, Britton and his colleagues have during the past 10 years steadily upheld the view that the regulation of carbohydrate metabolism was the "prepotent" function of this endocrine gland. A final solution of this problem is not yet available but the experimental facts now clearly indicate that the alterations in carbohydrate metabolism following adrenalectomy or the injection of cortical hormone into normal animals are of such a character that they can hardly be dismissed as of minor importance. Consequently, any theory of cortical function must link both the alterations in carbohydrate and electrolyte metabolism. Such an all inclusive theory is not yet available, but it would appear that the cortical hormone is related to some metabolic process which has a relationship in both these aspects of metabolism. Furthermore, consideration must be given to the observations of Long, Katzin, and Fry<sup>1</sup> that the cortical hormone also effects protein metabolism, particularly in fasting animals, in which a marked increase in the rate of tissue protein catabolism is brought about following its injection.

The main observations indicating that the adrenal cortex participates directly in the regulation of carbohydrate and protein metabolism are as follows:

(a) Adrenalectomized animals suffer depletion of their carbohydrate levels in liver muscle and body fluids (Long, Katzin and Fry; Britton and Silvette).

(b) Fasting adrenalectomized animals excrete less nitrogen than normal fasting animals (Long, Katzin and Fry; G. T. Evans).

(c) Phloridzinized-adrenalectomized rats excrete less glucose and nitrogen than intact animals (G. T. Evans).

(d) On exposure to low oxygen pressures, fasted normal rats increase their liver glycogen and urine nitrogen while adrenalectomized rats do not (G. T. Evans).

(e) Adrenalectomy alleviates a total or partial pancreatic diabetes.

(f) The injection of cortical extract or crystalline steroids isolated from the adrenal cortex into fasting adrenalectomized or normal animals is followed by striking increases in liver glycogen and by mild hyperglycemia. Since the muscle glycogen is unchanged, a new formation of carbohydrate must have taken place from noncarbohydrate sources and this source is apparently protein, since these also occur in increased nitrogen excretion of sufficient magnitude to account for the increased carbohydrate found.<sup>1</sup>

(g) The mild diabetes of hypophysectomized-depancreatized or adrenalectomized-depancreatized animals can be exacerbated by injection of cortical extract. Furthermore, the diabetes of partially depancreatized rats may also be exacerbated even to the point when fatal diabetic coma is precipitated.<sup>1</sup>

(h) Injection of cortical hormone or the adrenotropic hormone of the anterior pituitary will inhibit insulin convulsions in mice, apparently by increasing the quantity of carbohydrate in the body.<sup>25</sup>

(i) The rapid depletion of the carbohydrate levels of fasting hypophysectomized rats may be prevented by injection of cortical extract or, if already depleted, may be restored. This effect is also accompanied by an increased nitrogen excretion.<sup>1</sup>

The common denominator of all these varied observations would seem to be the effects on protein catabolism. In condi-

tions where this is proceeding at an enhanced rate, as in fasting, phloridzin or pancreatic diabetes, removal of the adrenal glands reduces the rate of tissue protein breakdown, thus not only reducing the nitrogen excretion but consequently the quantity of glucose made available to the organism. This is reflected by lowered carbohydrate levels in the liver and body fluids. Conversely, the injection of an excess of the hormone drives up the rate of protein breakdown, making available glucose from the catabolism of the resulting amino-acids. In depancreatized animals this results in an increased glycosuria and nitrogen excretion, so that it is fair to regard the cortical hormones as possessing "diabetogenic" activity.

The relationship between the anterior pituitary and adrenal cortex in their effects on metabolism is a complicated one inasmuch as the level of activity of the cortex is controlled by the corticotropic

hormone of the pituitary. Consequently, the injection of crude extracts of the latter may not only act directly on the tissues, apparently inhibiting glucose utilization, but may also by their stimulation of the adrenal cortex increase the rate of glucose formation. These 2 effects are of course found after removal of the pancreas and raise the important point that the diabetic syndrome may not only be produced by insulin deficiency but also by anterior pituitary and adrenal cortical hyperactivity.

It may be definitely concluded, however, that the adrenal cortex is an important member of the system of endocrine glands that regulate metabolism and while many questions remain unanswered, it would appear to be concerned with these processes by which glucose is made available to the organism at times when either the supply from other sources is deficient or when unusual demands are made for this material.

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## DIABETES

By FREDERICK M. ALLEN, M.D.

**Experimentation**—Among a mass of experimental work too vast to be reviewed, the rôle of the *anterior hypophysis* is still the outstanding development. The investigations throwing greater light upon the influence of the hypophysis, the adrenal cortex, and other glands serve also to confirm *pancreatic deficiency* as the central feature in diabetes. The injections of anterior pituitary extract, which produce a true permanent diabetes in animals, also cause hydropic degeneration of the islands of Langerhans.<sup>26-30</sup> The action is not merely upon the pancreas, because in totally depancreatized animals the hypophyseal injections increase the sugar production, while hypophysectomy markedly

ameliorates this and all other symptoms. Inasmuch, however, as hydropic degeneration is known to be the result of functional overstrain of the pancreatic islands, the hypophyseal excess evidently acts directly or indirectly to break down the beta cells of these islands by overstrain. Accordingly, even the diabetes of hypophyseal origin is still a pancreatic diabetes.

Further evidence is furnished by the fact that the hydropic changes in the islands are prevented if the animals receiving the hypophyseal injections are at the same time treated by 1 of 2 methods, *i. e.*, (*a*) fasting, (*b*) insulin injections. Also under these conditions no diabetes results. The scientific sup-

port of the treatment of diabetes by fasting or undernutrition is thus strengthened. In their most recent paper, Best and collaborators<sup>31</sup> also make interesting suggestions concerning future possibilities of preventing or curing the incipient stages of human diabetes.

**Diagnosis**—It remains a fact that if a suspected individual is given a *high carbohydrate diet* for a few days, and an analysis of blood and urine is then made within an hour after a meal high in starch and sugar, a sufficient excess of glucose will nearly always be found to reveal diabetes if present. When a more formal or positive test is needed, the *Exton plan* of giving 50 Gm. glucose and repeating it in  $\frac{1}{2}$  hour has received further corroboration<sup>32</sup> as being superior to the former single administration of a larger quantity. The essential point is that in a nondiabetic the blood sugar tends to fall after the second glucose dose, while in a diabetic it rises higher.

Incidental mention may be made of a simplified method of testing for glycosuria without the inconvenience of liquid or heat. The former Nylander reagent, consisting of an alkaline bismuth solution which is blackened by glucose, has been modified to a white powder and introduced commercially under the name of *galatest*. This powder darkens when merely moistened with sugar-containing urine. The test is not as delicate as the usual Benedict method and should not replace the latter, but is sometimes convenient for patients travelling or under other conditions.

**Complications and Mortality**—The vascular complications, particularly *gangrene*, remain as the most important practical problem because of their pre-eminence as causes of disability and mortality. The best recent discussion is in the latest edition of Joslin's textbook.<sup>33</sup> There has not yet been success

in establishing any single substance, such as sugar or fat, as a specific chemical cause. Although the influence of the diabetes itself is partially questioned,<sup>34</sup> this factor seems to be established by abundant evidence, including the experience with children in Joslin's clinic. "In the 150 cases with duration 15 years or more with onset in childhood, nearly 50 per cent of those studied have shown calcified arteries in the legs by roentgen-ray." The present writer regards prevention as the supreme practical consideration, inasmuch as efficient control of the diabetes seems capable of obviating these and other complications.

**General Therapy**—The prevailing treatment of diabetes is dominated broadly by 2 factors, *viz.*, the introduction of *high carbohydrate diet* and of *protamine insulin*. Physicians and specialists are divided into 3 schools:

(1) Those who insist upon normal urine and normal blood sugar and who use various devices for accomplishing this result, such as limiting the daily amount of carbohydrate (perhaps 100 to 150 Gm. total), dividing this carbohydrate into multiple lunches at various hours, using various combinations of protamine and regular insulin, or, if necessary, abandoning protamine insulin in favor of regular insulin. (Cf. Marks<sup>35</sup>.)

(2) Holders of intermediate views, ranging from those who allow hyperglycemia but not glycosuria, up to those who permit excretion of as much as 10 to 20 per cent of the ingested carbohydrate. All in this group hold the idea of controlling diabetes, but believe the moderate laxity to be justified by convenience, avoidance of insulin reactions, or supposed dangers in elderly patients or those with cardiac or vascular complications.

(3) A radical group who discard all established standards of diabetic control,

giving heed only to the amount of sugar metabolized and ignoring the amount excreted.

It is well known that recovery from wounds and infections can occur even when the sugar is high.<sup>36</sup> The Cornell Medical School has sanctioned a plan<sup>37</sup> of giving enough protamine insulin to assure subjective well-being and absence of polyuria, acidosis, or loss of weight, and completely disregarding continuous heavy glycosuria.

Insulin can cover so many blunders in treatment that it has given rise to many false conclusions. It is at least proper to remind practitioners that no treatment should be employed until it is supported by proof. No proof based

upon brief experience of 1 year or several years is adequate for diabetes. The benefits of thorough control are adequately proved. Inadequate control creates liability to progressive loss of tolerance and also various symptoms. Furthermore, every experienced therapist is apt to remember patients who, either with or without the use of various quantities of insulin, have come to him with the complaint: "Doctor, for 10 or 15 years I knew I had sugar in the urine, but I felt well, I didn't have weakness or thirst or loss of weight, the druggist never found acetone in my urine, and when I cut myself I healed up all right. Why should I now have this gangrene in my foot?"

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## HYPERINSULINISM (Hypoglycemia, hypoglycosis)

By FRANK N. ALLAN, M.D.

Hyperinsulinism and hypoglycemia have become important clinical problems in less than 2 decades. Contributions to medical literature under these titles have been rapidly increasing, but confusion still exists in regard to their interpretation. There is need to analyze the meaning of these diagnostic terms.

**Definitions** — The name "hyperinsulinism" implies overproduction or excessive action of insulin. Apart from administration of insulin, it can originate only from an abnormal pancreas which secretes more insulin than is needed by the body for its normal requirement.

Hyperinsulinism is manifested by hypoglycemia and the symptoms which accompany the fall of the sugar content of the blood to a low level. Yet hypoglycemia can occur from other causes and does not by any means invariably indicate hyperinsulinism. Furthermore, hypoglycemia of mild degree appears to be normal for some individuals, and

hypoglycemia of even advanced degree may occur without any symptoms. This term, therefore, does not indicate any true pathologic condition or clinical picture. It merely serves to classify the laboratory report of blood sugar estimation.

The term "*hypoglycosis*" is proposed by the Reviewer to apply to all the clinical phenomena which may result from abnormal decrease in the sugar content of the blood or body tissues. Since the diagnosis of spontaneous hyperinsulinism cannot be made with certainty without examination of the pancreas through surgical exploration or autopsy, it is necessary to consider together all the factors which may be concerned with hypoglycosis.

**Incidence of Hypoglycemia**—Many physicians are still inclined to consider the blood sugar probably abnormal when it is found below 80 mg. per 100 cc., and certainly abnormal when less than 70 mg. The study of the blood sugar

values made by John in 1928 should be recalled. In an analysis of 22,808 blood sugar determinations made in nondiabetic cases he found the figures 80 or less in over 15 per cent, and 70 or less in approximately 4 per cent. Eleven readings were 40 or under; the lowest was 30. These low values were apparently normal for the individual; there were no special complaints in the cases especially investigated. These observations have been confirmed recently by Hart and Lisa.<sup>38</sup> Routine fasting blood sugar tests were made for 21,000 patients. The blood sugar was below 80 in 11 per cent of cases. It was under 70 in 3.5 per cent, and in 18 cases was under 40; the lowest reading was 26. In only the latter case was the blood sugar test made at the time of an attack which was attributed to hypoglycemia. In all the other cases the patients were without any evidence of hypoglycemic shock; in none was hyperinsulinism discovered.

Rector and Jennings found that hypoglycemia without symptoms was even commoner in children. Among 572 children under 12 years admitted to the hospital for conditions unrelated to hypoglycemia the blood sugar was from 69 down to 50 in 43 cases, an incidence of symptomless hypoglycemia of 7.5 per cent. Hartmann,<sup>39</sup> and Miller and Ross<sup>40</sup> found that the blood sugar of newborn infants in the first 48 hours of life was frequently below 40, without symptoms. Tests made in the case of infants of diabetic mothers averaged lower but Miller and Ross concluded that the blood sugar does not seem important in relation to symptoms.

The great frequency of hypoglycemia without apparent clinical significance indicates the need for a term which can be applied where there is actually evidence of a deficiency of sugar. Hypoglycosis should serve as a suitable designation for

these cases in which low blood sugar is really accompanied by ill effects.

In contrast to the frequency of hypoglycemia, proven hyperinsulinism is rare. Including the first known case of hyperinsulinism due to islet tumor (Wilder, Allan, Power and Robertson), seen in 1926, there were only 12 cases at the Mayo Clinic up to 1939.<sup>41</sup> The total number of cases on record in 1940 was 96, according to Frantz.<sup>42</sup> Additional case reports appear from time to time from various sources but as yet few large hospitals have had more than 1 or 2 cases in which the diagnosis has been verified.

Although hyperinsulinism related to known organic disease is rare, it is thought by some that many of the cases of hypoglycemia represent functional hyperinsulinism. Whether this is true or not, conditions which may require consideration of hyperinsulinism are seen not uncommonly. It is difficult to determine the actual incidence of pathologic hypoglycemia or hypoglycosis because of varying standards of diagnosis and because the symptoms may be misinterpreted.

**Symptoms**—The faintness, nervousness, palpitation, sweating, peculiar sensations, mental confusion, loss of consciousness and convulsions resulting from hypoglycosis of any type are not pathognomonic. The variability and diversity of the symptoms make the clinical picture appear complex, but recognition of the disorder is simplified by a common characteristic which deserves emphasis, *i. e.*, the symptoms tend to occur when the stomach is empty and subside after eating, particularly when food or drink rich in sugar is consumed (F. N. Allan).

The various neuropsychiatric manifestations of hypoglycosis have been given special attention since insulin treatment of schizophrenia became popular. A

good summary of these problems has been presented by Moersch, writing with Kepler and with Kernohan.<sup>43</sup>

Angina pectoris suffered by 2 patients, presumably free from organic heart disease, was described by Weinstein and Mattikow,<sup>44</sup> when there was relatively slight depression in the blood sugar, reaching 54 in 1 and 52 in the other case. In the presence of coronary sclerosis it would be expected that angina pectoris might be precipitated readily by hypoglycemia, but such an experience seems to be rare. Heyn and Sommer<sup>45</sup> reported a case of islet tumor with hypoglycemic symptoms for 7 years, terminating in death from heart-failure. In this case the heart disease was probably independent of the hyperinsulinism, but the fatal breakdown may have been provoked earlier on account of the frequent recurrence of hypoglycemia attacks.

Persistence of neuropsychiatric symptoms and signs has been reported in an increasing number of cases in which there has been prolonged hypoglycemia either because of overdosage with insulin injections or because of spontaneous hypoglycosis. Mental deterioration, aphasia and hemiplegia have been described and post-mortem examination has shown multiple hemorrhages and degenerative changes affecting all parts of the brain. These changes have been described by Moersch,<sup>43</sup> Malamud and Grosch,<sup>46</sup> and Layne and Baker<sup>47</sup> and others. Freedman<sup>48</sup> observed hyperplastic changes in the pituitary in 2 autopsied cases of islet cell tumor, but clinical evidence of disturbed pituitary function was not apparent. The development of a persistent neurasthenic state has been described.<sup>49</sup> Whether this is also due to an organic change in the brain or whether it results merely from apprehension and worry on account of

the constant threat of disability and collapse is difficult to determine.

**Etiology**—Hyperinsulinism has been known to arise from islet tumors of the pancreas since the observation of the case reported by Wilder, Allan, Power and Robertson in 1927. In this case the tumor was malignant and metastatic lesions were present. Only 4 other such cases have been reported. The analysis of all reported cases of islet cell tumor with hypoglycemia, made by Frantz, has shown that malignant tumors are fortunately in the minority. The tumors were benign in 70 of 96 cases. Twenty-one others showed suggestion of malignancy, but in a large number of these followed for varying periods after excision there was no sign of recurrence and there is hope that not all were actually malignant.

The size of islet tumors varies tremendously. The smallest are microscopic; the largest on record weighed 501 grams and measured 9.5 by 8.5 cm. The average diameter is 1 to 2 cm. Multiple tumors have been observed in an important number of cases, and it is vitally important to consider this when surgical treatment is undertaken. In the first case in which double tumors were encountered (Judd, Allan and Rynearson), both were readily seen and removed, but in some cases when an apparently solitary tumor has been removed, failure to secure relief has led to a second operation and discovery of a second tumor, missed at the first. Whipple<sup>51</sup> found a pair of tumors in 3 of 15 cases. Four tumors were found in a case described by Conn.<sup>52</sup>

Hyperplasia of the islands of Langerhans in adult cases of hypoglycemia is rarely seen, but a case reported in 1939<sup>53</sup> has been added to those described earlier (John; Phillips). The observation of hyperplasia in infants born of diabetic mothers, described by Dubreuil, and

later shown to be related to fatal hypoglycemia by Gray and Feenster, has been repeated by Gordon.

An unusual case of hypoglycemia was cured by removal from the pancreas of a calcareous mass, measuring 2.5 by 3 cm. (Herrmann and Gins). Examination did not show any glandular secreting growth but presumably hyperinsulinism had been present, since the symptoms were related to the presence of this lesion in the pancreas.

In addition to islet tumor and islet hyperplasia, spontaneous hypoglycemia has been found in association with extensive liver damage and in cases with disease of the adrenals, pituitary and also the brain. Meakins<sup>54</sup> has described 3 cases in which hypoglycemia occurred after encephalitis, which later led to Parkinson's syndrome. As a rule, the evidence of the underlying disease outside of the pancreas had been clear cut, but Coller and Jackson<sup>55</sup> reported hypoglycemia attributed to hepatitis in association with gall-bladder disease in which the source of the trouble was discovered only after careful and detailed scrutiny. In their cases in which the liver damage had presumably not progressed far, there was recovery after operation for removal of the gall-bladder.

All cases without any evidence of organic disease have in some quarters been classified as functional hyperinsulinism. Harris is commonly given credit for discovery of "hyperinsulinism," and many publications refer to his report of 3 cases in which there were mild hypoglycemia symptoms, published in 1924. Yet as Whipple and Frantz, and Wilder<sup>41</sup> have pointed out, his observation of the relation of clinical symptoms to hypoglycemia was antedated by others (Parker and Finley; Gibson and Lorimer). Furthermore, there is doubt regarding the actual rôle of insulin and the pancreas in

these cases. Yet, Harris deserves great credit for making more widely known by publications and addresses, the clinical picture associated with abnormally low blood sugar.

**Diagnosis**—When symptoms suggest low blood sugar, the clinical impression must be confirmed by the blood sugar determination and the test must be made right at the time that the symptoms are present. Wilder has emphasized the importance of the fasting test. If this is below 50, it is likely to mean that the symptoms have an organic basis. If provocative measures, including muscular exertion and sugar tolerance tests, have to be employed to cause return of symptoms, they are likely to be mild and functional.

The character of the blood sugar curve in sugar tolerance tests is not a good guide in differential diagnosis. It is common for many normal people to have terminal depression of the blood sugar curve at the end of the test. Wheelon<sup>56</sup> found further that a depression from the start of the curve, usually of slight degree, occurred in over 20 per cent of sugar tolerance tests made in 698 cases of various types. Nervous instability was common in these cases but the relation of the blood sugar to the symptoms was indefinite. On theoretical grounds, a flat or falling curve of this type might be expected in hyperinsulinism. This has not been true in actual experience. Malamud and Grosch<sup>46</sup> found that in the reported cases of actual hyperinsulinism with islet tumor the dextrose tolerance was more likely to be high. Conn<sup>52</sup> found that the type of sugar tolerance curve was modified greatly by the type of feeding given beforehand.

After finding a low blood sugar test, it must be demonstrated that raising it to normal will relieve the symptoms. Then when the symptoms have been



identified with a low blood sugar level, the possible origin must be analyzed. Conn<sup>57</sup> has emphasized the value of detailed studies of liver function to differentiate hepatic hypoglycemia from hyperinsulinism. In the absence of gross evidence of disease it may be impossible to determine the cause without exploration of the pancreas.

**Treatment**—The *ingestion of sugar* or other *carbohydrate food* should relieve any symptoms related to actual hypoglycemia, but the problem in treatment is to stabilize the blood sugar level, and prevent their appearance. Increasing the carbohydrate content of the diet and adding lunches between meals and at night, to supplement the diet, is the most direct treatment. Yet the need for eating so frequently may be troublesome, and the results may continue to be more or less incompletely effective.

In mild cases, other adjustments of the diet are more helpful. *Restriction of carbohydrate intake*, and *increase in the fat content* have been used with success, and a *high protein diet* has also been recommended<sup>57</sup> Such diet plans are designed to reduce the stimulation of insulin production and to provide glucose for utilization more slowly and steadily. The use of small doses of *insulin* to prevent rise in blood sugar after meals, and the consequent stimulation of the endogenous insulin supply, proposed by John, has also been employed by others, with benefit in a small number of cases.<sup>58, 59</sup>

Surgical treatment must be considered when dietary management fails to prevent severe symptoms. There has come to be general agreement regarding the following indications for *exploration of the pancreas*: (1) Repeated fall of the blood sugar below 50; (2) simultaneous occurrence of severe symptoms, causing

disability in spite of attempts to relieve them by dietary regulation; (3) definite relation of the symptoms to the blood sugar level, shown by prompt relief after administration of sugar, and (4) exclusion of disorders affecting organs other than the pancreas.

The most comprehensive review of the results of surgical treatment was published by Whipple<sup>51</sup> in 1938. At that time he analyzed the results of excision of tumors in 56 cases on record. Brilliant relief was known to occur in all but 5 instances. In these cases there may have been a second tumor remaining in the pancreas; in fact, a second operation led to discovery of a second hidden tumor in several cases.

What to do if the initial exploration of the pancreas reveals nothing abnormal is a problem which must tax the judgment of the surgeon. *Resection of part of the pancreas* when a tumor has not been found had not proved of any great benefit in the earlier cases reported (Judd, Allan and Rynearson), but in a few cases in recent years, encouraging results have been claimed (Thomason; Graham; David<sup>60</sup>). If the decision to operate has been based on the 4 points listed above, the surgeon must be prepared for radical measures. If, however, surgical treatment has been undertaken with weak evidence for actual hypoglycosis, resection of the pancreas is certainly not warranted.

A unique form of treatment was undertaken by Walters in 1934. Not finding any tumor or other gross change in the pancreas, he placed a *ligature about the midportion of the gland*. The hypoglycemic symptoms decreased; later diabetes developed. No other reports of such treatment have appeared since then, no doubt because of the fear of the hazard from necrosis of the pancreas.

## OBESITY

By JOSEPH T. BEARDWOOD, JR., M.D.

It is of interest to note the continued interest in drug therapy, other than thyroid, in the treatment of obesity. It is also gratifying to observe the increased interest in obesity in children, and the various attempts made to evaluate and treat this condition. The question of impaired carbohydrate metabolism in obesity has been one that has aroused interest for some time.

Hubbard and Beck<sup>61</sup> report their observations on a series of 39 cases. No method of selection was used except that patients with diabetic symptoms were not studied. Otherwise, all patients presenting themselves at the clinic whose weight was reduced to an extent considered reasonably satisfactory and on whom the second dextrose tolerance was obtained after weight reduction have been included. Of the 39 patients, all but 2 were women from 25 to 72 years of age (average 44 years). The average time during which the patients took the diet before the tests were repeated was 350 days, with extreme values of 196 and 862 days. During this period they lost between 26 and 110 pounds (11.6 and 50 kg.); the average weight lost was 58 pounds (26.3 kg.). The proportion of patients who showed abnormal dextrose tolerance tests before weight reduction was 87 per cent but the degree of abnormality was not marked. After weight reduction, 90 per cent of the patients showed some improvement in the test and only 23 per cent showed any demonstrable abnormality. The improvement in dextrose tolerance appeared to be due to the weight reduction rather than directly to the diet, for (1) the change in the curve persisted when the amount of carbohydrate fed was increased; (2) it

was of a type which could not be explained readily by the ingestion of diets low in food value, and (3) it paralleled roughly the changes in weight.

**Obesity and Hypertension** — The relationship of obesity and hypertension is very important. Many extensive and exhaustive insurance statistical studies show that hypertension is associated with overweight and is usually in a direct proportion to the question of overweight. Wood and Cash<sup>62</sup> have attacked this problem from an experimental angle, and from these experiments it seems clear that both normal dogs and dogs with experimental hypertension produced by 2 different methods show marked increase of systolic blood-pressure when caused to gain large amounts of weight by feeding them a diet composed chiefly of beef fat. Though the final explanation of this rise in blood-pressure is not known, it seems most probable that it is intimately associated with the increase of body weight. This assumption is further supported by the fact that 2 dogs, whose weight was maintained by feeding raw beef only, showed no change in blood-pressure, while 1 dog, fed entirely on raw beef in amount sufficient to cause marked gain in weight, developed marked elevation of both systolic and diastolic pressure. Though it is of considerable added interest that the diastolic pressure of this latter animal showed such a marked rise during the period of excessively abundant high protein diet, their studies of the experimental conditions to which this dog was subjected are not yet adequate to justify further comment.

It has been of much interest to the REVIEWER that both groups of dogs, hypertensive and normal, gaining weight

on a high fat diet have shown a rise of systolic pressure only. This observation suggests that the hypertension of obesity is in some way fundamentally different from the hypertension experimentally produced by interference with blood flow through the kidneys, under which condition the diastolic as well as the systolic pressure is always elevated.

Weight reduction in patients has been followed by a fall in blood-pressure and symptomatic improvement. Although this particular phase of the discussion does not fall within the scope of this paper we are not unmindful of the fact that improvement following weight reduction is not based on systolic blood-pressure fall wholly, but mainly upon mechanical and chemical factors, particularly in reduction of cardiac work for exercise. This similarity in behavior of systolic blood-pressure relative to body weight in dog and man does not imply a causal relationship between obesity and essential vascular hypertension. Furthermore, the rapidity of forced weight gain and weight loss in these dogs partially invalidates any careful comparison with clinical experience. The true relationship of obesity to human hypertension remains to be shown, but an explanation previously suggested, that obesity may act mechanically to produce increased resistance in the peripheral vascular stream bed, seems most likely.

**Drug Therapy**—Ersner,<sup>63</sup> in a study of 500 cases, states that in obesity *amphetamine sulfate* has proved to be the "drug of choice" in obtaining excellent results. No serious complications were encountered. Only obese patients who gave a history of overeating were selected for treatment. After a physical examination the patient was put on a diet of from 1200 to 1500 Calories daily. This diet consisted of dry cereals, skimmed milk, tea or coffee (without

sugar or cream), fresh and stewed fruits, raw and cooked vegetables, 1 slice of bread with each meal and the choice of from 6 to 8 ounces of meat, fish, chicken, cottage cheese or 2 eggs daily. The patient was cautioned to limit the intake of fluid and to make certain of a daily evacuation. The patient was given the first week's medication (the smallest possible dose) and thereafter returned every week for a check-up and further medication. The drug was withdrawn at the end of every month or the loss of the first 20 pounds (9 kg.) and subsequent 15 pounds (6.7 kg.), and for the ensuing week some brand of vitamin B, C and G was prescribed to make up for any deficiency in the diet caused by the patient's carelessness. After each of these vitamin periods the previous week's dosage was again prescribed and then increased the following week. This permitted the final strength of the drug, one 10-mg. tablet after each meal, to be reached in about 3 months. The amount of weight to be lost at any 1 course of treatment was never to be more than one-fifth or one-sixth of the patient's greatest weight. If the new final weight was far from the nearest calculated normal chart weight (according to height and age), the patient was instructed to return in from 4 to 6 months, when again this procedure would be repeated. Thus, no patient in the series showed any untoward effects from the loss of weight, even though as much as 60 pounds (27 kg.) was lost by 1 patient in the course of 3 months. The average weight lost for the first week amounted to 5 pounds (2.3 kg.). The average loss for a course of treatment (from 3 to 12 weeks) was 3½ pounds (1.4 kg.) per week.

With the exception of the vitamin week, there were but few occasions when a continuous and sustained loss of weight

was not obtained: 100 per cent co-operation was requested. Invariably most of the patients would voluntarily say that they were feeling much better or had much more pep. All agreed that the loss of appetite made dieting easy. With the small graduated doses of amphetamine sulfate employed, the systolic and diastolic readings, when hypertension was present, usually dropped to normal. Whether this drop toward normal was directly due to the action of the drug or to the loss of weight is a question. Several instances of hypotension became normal during the course of treatment. Normal blood-pressures were not affected or were slightly, if at all, lowered. There was but little change in the metabolic rate during the course of treatment. A marked progressive improvement in urines containing albumin, sugar and hyaline and granular casts was observed, indicating that amphetamine sulfate produces no injurious renal effects.

There was little evidence of true addiction. In most instances, the medication caused a mild constipation, which was easily remedied with a mild laxative or a simple lubricant, as liquid petrolatum. The reported untoward reactions of the drug should be of much significance to the dispenser and the novice who is about to prescribe it. The patient must be educated as to the possibility of its allergic reactions and of its cumulative effects. Self-medication and overdosing must be eliminated to prevent any future fatalities.

### Obesity in Children

In a report made by Kunstadter,<sup>64</sup> he states that whether a state of obesity is a result of an hereditary or constitutional factor, hyperalimentation or an endocrine disturbance, a state of over-nutrition exists for the particular obese child, *i. e.*, there is an excess of intake

over the caloric requirement. It is extremely difficult to obtain the co-operation of a child in exercising his will power, which makes a careful consideration of the emotional or psychologic aspects of treatment highly important. In cases of children of the Jewish race, the hereditary factor must be considered, since they are known to have a relatively high incidence of obesity. Parents often encourage their children to eat, believing that a fat child is healthy. An attempt was made to get full co-operation from the parents so that they might encourage their children in the difficult task of adhering to a reducing diet. To the older children they explained the purpose of the diet, particularly with respect to health and a presentable appearance. Despite the use of a bulky high protein diet and thyroid extract for many patients, appreciable weight loss was the exception rather than the rule. In fact, the use of thyroid extract frequently increased the appetite, and weight gain was not unusual unless the drug was increased to the point of tolerance. The major problem, therefore, was "How can the appetite be controlled so that a prescribed reducing diet will be adhered to?"

**Treatment**—Recently, Lesses and Myerson found that when *benzedrine sulfate* was administered to various psychotic adult patients, frequently there resulted a decrease in the appetite, a disappearance of the feeling of fatigue, and a beneficial influence on the state of mind. With the decrease in appetite, there resulted voluntary dietary restriction, and weight loss occurred in many patients.

In view of the fact that the obesity of adults frequently begins in childhood because of faulty food habits, and because co-operation by children is difficult to obtain, a therapeutic measure that might be of some help in the management of

this problem should be gratefully received by the pediatrician. It is true that a great number of preadolescent obese children outgrow their obesity spontaneously, due to an apparent self-regulation of their neuroendocrine system which usually occurs during the transition from childhood to adulthood, nevertheless, a large proportion of obese children do not outgrow their obesity and require medical aid.

Benzedrine sulfate was administered to 30 obese children between  $2\frac{1}{2}$  and 16 years of age. These children were selected after they failed to lose weight on a prescribed reducing diet. Many, in addition, had received thyroid extract. At first the drug was cautiously administered in small doses. After trial it was found that these were ineffective so that  $\frac{1}{12}$  grain (5 mg) was chosen as the initial dose, gradually increasing to what was considered an optimal effective dose according to the effect upon appetite and weight loss. The drug was administered either 2 or 3 times daily, before breakfast and lunch, and after school, if a third dose was given. The evening dose was avoided so that sleep would not be interfered with. The maximum daily dose prescribed for any 1 patient was  $\frac{5}{8}$  grain (50 mg) to a 14-year-old male weighing 168.5 pounds (76.6 kg). The majority received a daily dose of from  $\frac{1}{8}$  to  $\frac{1}{2}$  grain (10 to 30 mg). Many of the children in the series took as much of the drug as was usually prescribed for adults, without untoward symptoms. For this reason the optimal dose cannot be estimated on the basis of either age or body weight. It is generally agreed that a definite tolerance to the drug not uncommonly occurs, so that, to be effective, the dose must frequently be increased. However, most reports state that it seldom is necessary to go beyond  $\frac{5}{8}$  grain (50 mg) a day, and the op-

timal daily dose for the average adult patient usually does not exceed  $\frac{1}{3}$  grain (20 mg).

In this series of children, the average weekly loss of weight of 26 patients who received continuous treatment for over 2 weeks was 0.831 pounds (0.377 kg). The greatest weight loss occurred during the first 2 weeks of treatment. There was little or no variation in the basal metabolic rate while under benzedrine treatment. Forty per cent of patients experienced unpleasant reactions at the onset of treatment. However, withdrawal of the drug was necessary in only 4 instances because of severe reactions. The optimal effective dose for obese children was apparently between  $\frac{1}{8}$  and  $\frac{1}{2}$  grain (10 and 30 mg) daily. Weight loss was primarily due to loss of appetite with subsequent decrease of food intake. Improvement in the state of mind with increase of will power, was probably a contributory factor. Withdrawal of the drug or decrease in the dose usually resulted in a return of appetite and an increase in weight.

Tolerance to the drug developed frequently, requiring gradual increase in the dose. Treatment of these cases should always be under the supervision of a physician. Examination of the blood of some of these patients revealed no significant variations in the blood picture for the use of the drug. Because of the report of Friedenberg relative to addiction to the drug, careful observation was made in this series but revealed no actual craving for the drug although several patients stated that they believed it helped them with their dieting.

### Obesity and Hypogenitalism

Cervino<sup>65</sup> studied children between the ages of  $7\frac{1}{2}$  and 14 years, 9 of whom were boys, in whom obesity was associated with hypogenitalism. Some of the

cases presented symptoms resembling Frohlich's syndrome; others were differentiated from the Frohlich type by a generalized distribution of adipose tissue and an exaggerated development of bones and muscles. Others, again, belonged to an intermediate type. Hypogenitalism in the cases simulating Frohlich's syndrome was restored to normal conditions at puberty or later if retardation of puberty occurred. The various features of the clinical picture, including personal and familial antecedents, age of onset, evolution, genital pathology, secondary sex characteristics and gynecomastia, are discussed.

Obesity with hypogenitalism dissimilar to Fröhlich's syndrome was found to date from birth or develop with the growing child, to continue after puberty, and either to undergo no modifications or to increase or decrease. In these patients the head was large, the cheek bones and chin pronounced and the diameter of the thorax and pelvis large for the age and body build. The feet gave the impression of a flat-footedness that was only infrequently confirmed roentgenologically. Heredity played a significant part. There was also precocity in dentition and in the ability to walk and talk. The general health was good. The appetite was exaggerated but did not show the predilection for certain foods noted in the cases resembling the Fröhlich type. Laboratory tests indicated normal levels of glycemia or a tendency to hyperglycemia.

The author regards obesity with hypogenitalism as due to modifications of the neurohypophyseal system. While the destruction of the anterior lobe by itself has not been demonstrated to induce adiposity, almost always damage to the hypothalamus is concomitantly observed. Damage to the anterior lobe could produce hypogenitalism with low physical

stature but not obesity. In the intimate connection between these 2 organs lies the explanation of many of the symptoms observed in these cases.

The transitory cases resembling Fröhlich's syndrome may be due to damage done to the hypothalamus if the regulatory processes of fat, carbohydrate and water metabolism are lodged here. At the same time the function of the hypophysis (anterior lobe) may be normal or excessive. In retarded puberty cases there may exist a temporary hypofunction of the hypophysis. Cases unlike the Frohlich syndrome in which, beside obesity, there is also seen a pronounced development of bone and muscles and occasionally a temporary hypogenitalism, suggest *hypercorticalism*. However, a functional increase of chromophil cells of the anterior pituitary may be involved. ***Restriction of carbohydrate and fat consumption*** gives better results in cases dissimilar to the Fröhlich type than in those resembling it.

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## RESPIRATORY SYSTEM

*Edited by* FRANK W. BURGE, M.D.

## CHEMOTHERAPY IN PNEUMONIA

*By* W. PAUL HAVENS, M.D.

The early favorable reports on the use of *sulfapyridine* in pneumococcic pneumonia have been confirmed. Marriott<sup>1</sup>

has summarized the collective results in 1991 treated patients with a mortality of about 5.5 per cent. At the same time,

surprisingly low mortality rates have been reported<sup>2</sup> following serotherapy, so that at the present time there is no evidence to prove the superiority of one form of treatment over the other in relation to mortality. It is to be expected, however, that the added trouble and expense of administering serum will render chemotherapy the method of choice provided equally good results and few hazards can be demonstrated consistently for the latter mode of treatment. At present several authorities advise the use of sulfapyridine in the uncomplicated case of lobar pneumonia but suggest specific immune serum when (a) sulfapyridine has been given 18 to 24 hours without improvement; (b) the patient is over 40 years of age; (c) the patient is pregnant or in the early puerperium; (d) more than 1 lobe is involved; and (e) when the blood culture is positive.

More recent developments in the search for chemotherapeutic agents which are less toxic for the patient and more effective against bacteria have resulted in the synthesis of the thiazole derivatives of the sulfonamide group.

During the past year the writer has been using **sulfathiazole** exclusively in the treatment of pneumococcic pneumonia. Experimentally, the toxicity of sodium sulfathiazole is less than that of sodium sulfapyridine when injected into animals. Sulfathiazole is more readily absorbed into the gastrointestinal tract, more rapidly excreted in the urine, and is conjugated in much less degree. In these respects it resembles sulfanilamide more than sulfapyridine. At present, sulfathiazole appears to be equally as effective as sulfapyridine in the treatment of pneumococcic infections and more effective against staphylococci. Its main advantage is the lower incidence of nausea and vomiting, occurring in 20 per cent of patients as opposed to the

incidence of 60 per cent when sulfapyridine is used. Other toxic manifestations of the 2 drugs are approximately the same in kind and frequency of occurrence. Because sulfathiazole has been equally effective and causes less nausea and vomiting, it has become the drug of choice in the writer's hands. The following discussion is concerned with the use of this drug although what is said may be equally well applied to sulfapyridine.

**Modern Management of Pneumococcic Pneumonia**—The diagnosis of pneumococcic pneumonia is made presumptively on the basis of a history of sudden onset with chill, fever, cough, pain in the chest, and rusty sputum, even though the physical signs be minimal early in the course of the disease. Immediately following the taking of the history and the physical examination, a blood culture is made, sputum is sent to the laboratory for bacteriological examination and typing and a blood count is made. If possible, a roentgenogram of the chest is taken at this time. Depending on the size of the patient and the severity of the illness, 30 to 60 grains (2 to 4 Gm.) of sulfathiazole are given by mouth at once while waiting for the completion of the bacteriological study of the sputum. Doses of 15 grains (1 Gm.) of the drug are given every 4 hours night and day. If in the ensuing few hours it is learned that bacteria other than the staphylococcus, hemolytic streptococcus, or pneumococcus are the cause of the disease, no more drug is given. If, however, type specific pneumococci, particularly of Types I, II, III, V, VII, VIII and XIV, are found in the sputum chemotherapy is continued and if any of the previously mentioned complications are present serotherapy may be started.

Although pneumonia may be caused by a variety of organisms, it is suggested



that the use of sulfathiazole be reserved for those cases of clinical lobar pneumonia caused by the hemolytic streptococcus, staphylococcus or pneumococcus of one of the following types (I, II, III, V, VII, VIII, and XIV), since these are the most invasive and the most common causes of typical lobar pneumonia. The presence of the higher numbered types of pneumococci in the sputum of persons, who, after a cold, develop fever, cough, râles in the chest and roentgenographic evidence of atypical pneumonia does not justify the use of chemotherapy unless there are definite indications that the pneumococcus is operative. At least 50 per cent of healthy individuals carry these higher numbered types of pneumococci in their mouths habitually, so that they are usually of no etiologic significance and may be merely coincidental findings in a patient whose pneumonia is caused by an organism not likely to be influenced by sulfathiazole. Personal experience has shown that all of these patients with influenza or influenza-like involvement recovered without specific therapy.

Even though one of the lower type pneumococci cannot be found at once in the sputum of a patient with a typical history of sudden onset with chill, pain in the chest, fever, cough, rusty sputum and leukocytosis, it is felt that specific chemotherapy should be started immediately. Too much weight cannot be placed on the importance of the history typical of lobar pneumonia. Subsequent examination of the sputum or examination of the peritoneal washings of a mouse injected with the sputum may afford the information as to which organism is the probable etiologic agent. Conversely, there does appear occasionally in the sputum of a person who has evidence of atypical pneumonia with a cold, cough, fever and râles in the chest,

a pneumococcus of the lower numbered types. In this instance, it is advisable to treat such a person with sulfathiazole in the event that the organism may become invasive.

**Dosage**—Sulfathiazole is more rapidly absorbed and excreted than sulfapyridine so that greater care must be taken to maintain an adequate amount in the blood. The optimal effective level of sulfathiazole in the blood is still uncertain and various workers place it between 2 to 10 mg. per 100 cc. of blood. The usual dose for the adult is 30 to 60 grains (2 to 4 Gm.) by mouth initially, followed by 15 grains (1 Gm.) every 4 hours. There remains some question as to how long such therapy should be continued. Some clinicians discontinue treatment after 24 hours of normal temperature while others continue to give the drug in diminishing doses for 7 to 8 days after the onset of disease. In the writer's experience, therapy has been stopped after 24 hours of normal temperature without untoward effect. The total amount given ranges from 360 to 600 grains (24 to 40 Gm.), depending on the reaction. For children, the daily dosage averages 1 to  $1\frac{1}{2}$  grains (0.06 to 0.1 Gm.) per pound of body weight.

It is always desirable to give the drug by mouth. However, if it is necessary to attain an effective level of the drug in the blood quickly because of severity of the disease or if the oral route is impossible because of nausea or vomiting or inability to take anything by mouth, the parenteral routes may be employed.

The relative insolubility of sulfathiazole makes it necessary to use the more soluble sodium salt.

Solution for subcutaneous use may be made according to the method of Taplin<sup>3</sup> by dissolving from 45 to 105 grains (3 to 7 Gm.) of *sodium sulfathiazole* in 1000 cc. of physiologic saline. The

amount given depends on the weight of the patient, the kidney function, and the state of hydration. The solution is prepared by heating physiologic saline to boiling and allowing it to cool for 5 minutes. Sodium sulfathiazole is then added and the solution is allowed to cool to room temperature. It may be allowed to run in subcutaneously at the rate of 200 to 300 cc. per hour. Depending on the response of the patient and the level of the drug in the blood, this dose may be repeated in from 24 to 30 hours. The average adult requirement to maintain an effective level in the blood is from 90 to 120 grains (6 to 8 Gm.) a day. It is advisable to allow the required amount of solution to run in at regular 6-hour intervals. Although this solution cannot be sterilized because sodium sulfathiazole is not heat stable, there have been no local reactions observed.

If it is desired to give sulfathiazole intravenously, the method of Long and Wood<sup>4</sup> for administering sodium sulfapyridine can be used. The dose of sodium sulfathiazole is 1 grain (0.06 Gm.) per kilogram of body weight. This is dissolved in enough sterile distilled water to make a 5 per cent solution. As for subcutaneous use, this solution cannot be sterilized; however, the pH is 10.7 to 10.8, so that it is bactericidal in some degree. This solution is allowed to run in intravenously at a rate not exceeding 5 cc. per minute. The dose may be repeated in 6 hours if necessary. If the drug cannot be taken by mouth at all, the intravenous and subcutaneous routes may be combined. It is important to remember that the 5 per cent solution for intravenous use is extremely irritating and will cause severe tissue damage if the needle gets out of the vein.

At times in the severely sick patient who can take sulfathiazole by mouth it is advisable to supplement this with an

initial dose of the drug intravenously calculated on the above scale, in order to raise the level in the blood immediately. This may be repeated in 4 to 6 hours, but usually an effective level is established by this time.

While chemotherapy is being carried on, the level of the drug in the blood should be measured daily and the concentration kept between 2 and 10 mg. per 100 cc. of blood. It is further recommended to examine the urine for blood, count the erythrocytes and leukocytes, and measure the hemoglobin daily in order to be aware of any severe change which might indicate the onset of an untoward reaction to the drug.

Ordinarily there is clinical improvement with decline of temperature in 24 to 48 hours following the administration of sulfathiazole for pneumococcic pneumonia.

If after 48 hours no improvement is noted, further search for some other cause of disease should be made and if after maintaining an effective level in the blood for 3 or 4 days no benefit is observed, the drug should be stopped. Frequently in such cases the additional burden of drug poisoning is added to the patient sick with a disease against which sulfathiazole has no effect.

**Toxic Reactions**—Toxic reactions which may be dangerous include acute hemolytic anemia, jaundice, agranulocytosis, renal calculi, hematuria, erythema, and fever. Headache, nausea, vomiting, and cyanosis, unless severe, are no more than troublesome. The occurrence of any toxic reaction classified as dangerous contraindicates using the drug again. Although agranulocytosis may be a manifestation of drug toxicity, an initially low leukocyte count is no contraindication to intensive therapy. It has not infrequently happened that the leukocyte count was low due to the overwhelming

infection and when this was controlled by chemotherapy the leukocytes increased in number.

In case of toxic reactions, *fluids* should be forced to encourage the elimination of the drug. Various successful efforts have been made to control the nausea and vomiting. *Nicotinic acid* in amounts of  $\frac{5}{8}$  grain (50 mg.) with each dose of sulfathiazole is at times effective. *Soda bicarbonate* given in 15 grain (1 Gm.) doses may help and giving sufficient sedatives in the form of *choral hydrate* or one of the *barbituric acid* derivatives may dull the preceptions to the point of being less aware of the unpleasant symptoms. *Increasing the fluid intake*, either by mouth or intravenously, omitting an occasional dose of the drug, or suspending  $7\frac{1}{2}$  to 15 grains (0.5 to 1.0 Gm.) of sulfathiazole in 1 dram (4 cc.) of *mucilage of tragacanth* at each dose are all methods of attempting to allay nausea and vomiting.

### Atypical Pneumonia

In 1939, Reimann and Havens<sup>5</sup> reported studies on a widespread influenza-like epidemic infection of the respiratory tract. Of 407 patients who were sick, 87 per cent were mildly ill. Six per cent were confined to bed with nasopharyngolaryngotracheobronchitis and another 6 per cent had pneumonia. Those with pneumonia manifested the same general symptoms as those with the milder form of the disease with an insidious onset, cough, scant sputum, photophobia, substernal pain, sweating, headache and weakness. Physical signs in the chest consisted of occasional dullness to percussion with suppression of breath sounds. Râles were almost always present in the interscapular areas or the lobes involved. Roentgenograms of the chest usually showed localized or diffuse areas of den-

sity where abnormal signs were found. Fever lasted on the average from 2 to 17 days in these patients with an average of 8.2 days. The number of leukocytes was usually normal or slightly increased towards the end of the disease. Blood cultures were sterile. Attempts to isolate an etiologic agent were uniformly unsuccessful, although from 2 patients observed in 1938 a filtrable infectious agent was recovered which when inoculated into animals caused a bacteria-free pneumonia characterized by an inflammatory reaction of the interstitial tissue of the lungs with a mononuclear cell exudate and often encephalitis. Unfortunately, the agent disappeared during passage in animals and proof of its etiologic relationship could not be substantiated. Pneumococci appeared rarely in the sputum and when present were thought to have no relationship to the disease. Chemotherapy was tried in a few patients and proved to be of no value. All patients recovered without specific therapy. Similar epidemics were observed in Massachusetts,<sup>6</sup> Texas,<sup>7</sup> Baltimore,<sup>8</sup> and New York,<sup>9</sup> and at the same time outbreaks of clinically similar diseases were reported by Horsfall<sup>10</sup> and by his associates which were proved to be true epidemic influenza.

Differentiation of these clinically similar entities is possible only by means of special study. Recently, Francis<sup>11</sup> reported the isolation of a virus from patients in a localized epidemic of 1940. The disease and the virus closely resembled influenza and its virus but were not identical with it. To differentiate them the one discovered first was called *Influenza A* and the one discovered in 1940 *Influenza B*. Recently another outbreak of pneumonitis occurring among workers at the National Institute of Health at Washington, D. C., has been described<sup>12</sup>

with clinical and roentgenographic similarities to the other respiratory tract diseases, but having as etiologic agent a

rickettsia identical with that previously isolated from cases of "Q" fever. Chemotherapy had no effect in these patients.

## PNEUMONOCOONIOSIS

By ROSS K. CHILDHEROSE, M.D.

Discussing the present status of silicosis, Lanza<sup>13</sup> estimates that there are at least 500,000 persons exposed to silica dust in the various industries in this country, but the Public Health Service believes that this figure is nearer a million. It can readily be understood, therefore, that the reservoir from which cases of pneumoconiosis might be drawn is immense. The increased importance of this disease is attested by the voluminous literature, and the many compensation laws enacted by governmental authorities throughout the world.

**Diagnosis**—Attention is called by Taylor and Hyman<sup>14</sup> to the essential requirements for a diagnosis of pneumoconiosis. This must be based on occupational history, present illness, physical and roentgen examinations, and laboratory studies. The factor of prime importance in the diagnosis is the history of exposure to siliceous dust, and a detailed occupational history is essential. This should include in chronologic order; the length of time spent in each position; the type of work performed; and the protective measures, if any, that were used. For example, to record that a certain patient was a miner is not enough. It is necessary to ascertain what type of work the man did in the mine; what minerals were mined; the number of years spent underground; and whether he used a dry or wet drill. An estimation of the dust concentration in his working conditions is desirable.

**Differential Diagnosis**—The various pulmonary lesions simulating pneu-

monoconiosis sometimes are confusing, and a careful consideration of the following points are helpful<sup>15</sup>

(a) *Chronic Passive Congestion from Cardiac Decompensation*—The increased linear markings of this lesion closely resemble those of an early stage of pneumoconiosis in that they are bilateral. There is, however, usually a history of heart disease, and the roentgenogram may reveal an enlarged heart.

(b) *Bronchiectasis*—A confusion may arise between this and an early pneumoconiosis in that there are bilateral increased markings, but the accentuation of these markings is more prominent in the lower lobes rather than in the midzones, and there is a history of cough with profuse expectoration.

(c) *Tuberculosis*—While this disease is frequently bilateral in extent, yet a major portion is commonly found in 1 lung, and a displacement of the trachea or, in severe cases, of the mediastinum by traction of fibrous tissue or lobular atelectasis to one side, will generally confirm a suspicion of tuberculosis. The characteristic feature of pneumoconiosis on the roentgenogram is its uniformly bilateral distribution. Any deviation from this, particularly if the abnormal shadows are congregated in the upper third of the lung field on 1 side, points to a tuberculous infection.

(d) *Acute Miliary Tuberculosis*—The patient is seriously ill, and a series of films, made 3 or 4 days apart, will readily differentiate it from pneumo-

coniosis, because in acute miliary tuberculosis the disease progresses rapidly

(e) *Metastases from Neoplasms*—

If the nodules are small and more or less uniformly distributed, they may resemble the nodules of silicosis. Without a clinical history or knowledge of the primary malignancy, they are very difficult to differentiate. As a rule, metastases are of different sizes, and rarely give the uniform distribution of the silicotic nodulation. The latter reaches its maximum amount in the central zone of each lung.

**Pathology**—Cole and Cole,<sup>16</sup> in an excellent monograph on pneumoconiosis, point out that the characteristic feature of fibrosis in silicosis is really a deposit of collagen, and certainly not fibrous reparative connective tissue. "This collagen is not readily differentiated from other lung tissues, even from smooth muscle tissue in the walls of blood-vessels, by the conventional hematoxylin and eosin stain, but when adjacent serial sections are stained with Mason's trichrome stain, the collagen takes on a brilliant blue in contrast to the red of the muscle, and the purple or rather dull blue of the other structures." They point out that collagen is laid down in laminae around blood-vessels and bronchi. When deposited around the walls of the terminal bronchioles, the constriction may cause a valve-like action, resulting in overdistended lobules, and eventually small cysts. Collagen is also deposited in masses with a whorl arrangement, and thus produces the well-known silicotic nodule.

The so-called "*acute silicosis*," fortunately, is not common, but may be found under working conditions that tend to liberate excessive quantities of exceedingly fine pure silica. The dusting is so overwhelming that the usual protective mechanism fails to handle the situation,

and an acute inflammation arises within the lungs. Gardner<sup>17</sup> states that the gross examination of the lungs reveals no nodules, but that there is a generalized partial consolidation of the lungs with the air spaces filled with actively proliferating phagocytes. The condition may develop in from 2 to 3 years, and death is due usually to tuberculosis.

**Tuberculosis and Pneumoconiosis**—Necropsy studies show that about 60 per cent. of silicotic patients die from tuberculosis. Some writers have gone to the extreme in stating that silica produces little disability in the absence of infection.<sup>18</sup> It must be said, however, that such statements are not borne out by necropsy findings. There is too great a tendency to diagnose tuberculosis as a complication in patients having advanced pneumoconiosis. Careful studies such as that reported by Taylor and Alexander<sup>14</sup> show that the incidence of tuberculous infection is about 60 per cent or less. They believe that, if the sputum is persistently negative for tubercle bacilli, active tuberculosis can be excluded, and that the type of tuberculosis that may be found is of the caseous pneumonic form. These results agree with the personal observations of the writer among the hard coal miners of Pennsylvania.

**Treatment**—Recent literature has referred to experimental work on the use of *positively charged metallic dusts*,<sup>18</sup> such as *metallic aluminum, iron* and *magnesium* for *prophylaxis*. Most of this work has been done at the University of Toronto, Ontario.<sup>19</sup> The admixture of aluminum dust in concentrations of less than 1 per cent will inhibit the development of silicosis. However, the idea is still experimental, and it would seem more reasonable to make every effort first to reduce the dust hazard in an industry than to complicate the dust-

ing by the addition of any such inhibitive agent.

### Asbestosis

In a report of 180 cases of asbestosis, Stone<sup>20</sup> points out that the average length of exposure of stage 1 patients was 8 years; stage 2 cases required 10 years; while that of stage 3 was 11 years. The outstanding symptom in all cases was that of dyspnea, while those in stage 3 complained of fatigue, cough, expectoration, tightness in the chest, and some loss of weight. The physical findings were that of emphysema at the apices, and a basal fibrosis. The most prominent physical sign was restricted chest expansion. The roentgenogram

was indispensable in the diagnosis, and the characteristic finding in it was an increased density in the lower zones, an indistinct diaphragm, obliteration of the costophrenic sulcus, and a fine lace network of interstitial or perivascular fibrosis. This was accompanied by a "ground-glass" or granular appearance in the mid-lung and bases.

The complication of tuberculosis was uncommon, but bronchitis, bronchiectasis, and bronchopneumonia were more frequent. In advanced cases of asbestosis, there was, very commonly, hypertrophy of the right ventricle and heart-failure. It is believed that the dyspnea of asbestosis is of cardiac or circulatory origin rather than pulmonary.

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## PULMONARY TUBERCULOSIS—PATHOLOGY AND PATHOGENESIS OF TUBERCULOSIS

By EDWARD R. BALDWIN, M.D.

The recent literature on the pathology and pathogenesis of tuberculosis has related chiefly to the question of primary and subsequent infections.

Sweany<sup>21, 22</sup> and his associates have published a number of carefully studied autopsies (130 cases selected from 1000) where the history indicated heavy exposure to continued infection. From the clinical, x-ray and pathological findings, 57.1 per cent of these seemed to have developed from the primary lesions by extension, *i. e.*, endogenous spread either continuous or in stages. In addition, 17.5 per cent were probably endogenous, and 25.4 per cent exogenous.

Estimates of the latent period from primary infection to clinical disease averaged 10 years. There were 35.7 per cent foci of primary complexes developed after 15 years of age with little involvement of regional lymph-nodes. The

conclusion is reached that most clinical disease in the first half of life arises from extension of primary infections, but the gradual loss of acquired immunity leads to exogenous reinfections, as indicated by more small healed foci having no connection with obsolete primary lesions.

A somewhat similar and exhaustive pathological study forms the subject of a monograph by Terplan.<sup>23</sup> It covered 700 children and 289 adults. The author, for 11 years an associate of Anton Ghon of Prague, but now in Buffalo, New York, first deals with the confusion caused by the incorrect use of terms "reinfection" and "superinfection" for extensions of the primary infections; likewise "childhood" and "adult" types of infection, whereas he finds no such distinct differences in the lesions. He would restrict the term "reinfection" to new exogenous foci.

Recent more careful studies indicate that many adults acquire primary infections and their course does not always conform to the immunological theories of Ranke. Of the 289 adults sectioned, only a few had died of tuberculosis. X-ray and series sections were made of many small foci. In adults, aged 25 to 54 years, typical primary complexes were found with no connections with some very old foci in different lobes, healed and obsolete. In 5 adults with healed primary foci, no involvement of regional nodes was found after serial section. Only true reinfection can produce a typical primary complex without involvement of regional nodes. Such reinfections can be found, evidently acquired at varying intervals; hence, multiple old calcified lesions in later life are not necessarily primary. Among the 700 children sectioned, aged 1 month to 18 years, 10 cases are noted where several reinfections from exogenous sources could be assumed. Others were entirely healed and no bacilli could be found in sections. The study represents a painstaking labor of 8 years and indicates that no hard and fast differences exist be-

tween first infections and subsequent and true reinfections.

A valuable x-ray and tuberculin test experience with children in Detroit, Michigan, was published by Johnston<sup>24</sup> and his associates, which reveals the difference between frequent exposure to infection and only accidental contacts. Among 828 children reacting to tuberculin and removed from homes which were unsuitable, or where exposure was possible, to foster homes for periods up to 12 years, only 33 developed further signs of progress of the primary disease, 23 after contact with a known source of infection was broken. All but 2 have recovered. Many of the endogenous spreads were during the adolescent period. Metabolism tests were made that showed lowered nitrogen retention in the presence of puberty in girls. Tuberculin sensitiveness lessened in the course of calcification of tubercles and was lost in 26 cases when the process was completed. The authors consider the test valuable in determining those children who should be followed in adolescence by x-ray examinations and other tests such as basal metabolism.

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## SURGICAL TREATMENT OF TUBERCULOSIS

By RALPH C. MATSON, M.D.

### Extrapleural Pleurolysis with Pack (Author's Method)

This operation was originally developed for the closure of residual cavities following thoracoplasty. The results were so satisfactory that the writer decided to employ it as a primary procedure in many cases where a partial thoracoplasty, or apicolysis, or even an extrapleural pneumothorax was under consideration. The technic of the operation is identically the same as extra-

pleural pneumothorax up to the point where an adequate extrapleural space has been created. Then, instead of closing the wound and resorting to subsequent refills of air or oil, the following procedure is employed:

**Technic**—All bleeding having been controlled with the high frequency current, the extrapleural space is irrigated with warm normal saline solution and suctioned dry. A sheet of *flexi-tissue* 2 feet square, previously sterilized by soaking it in 1:1000 *mercuric cyanide solution* for 30 minutes, is rinsed in sterile

water, placed flat over the operative wound and then, first with the fingers and next with long curved sponge forceps, is pushed into the extrapleural space in such a manner that the entire space is lined with the tissue, leaving the folded portion emerging from the chest wall opening like the neck of a sack. The sack is now packed with 1 per cent *gomenol gauze* (see later). Again, using first the fingers and then long sponge forceps, the gauze is packed in a circular manner, beginning at the base from the front to the back laterally and medially. As the pack approaches the dome of the stripped lung, selective pressure is made, depending upon the size of the underlying tuberculous cavity. After the sack is snugly filled to the level of the chest wall, a short-looped decnatol tie is placed at the end of the gauze to facilitate its removal. The portion of the sack emerging through the chest wall is grasped in the hand and closed as one closes a paper sack. Two heavy smooth blade forceps are clamped on each side of the neck of the sack at the inner chest wall level. These clamps are placed as close to the packed gauze as possible. This facilitates a snug closure of the sack with 2 No. 6 decnatol ligatures placed medial to the clamps, which prevent the decnatol ties from slipping distal. As the first tie is tightened, the clamps are removed and a second tie is then placed to reinforce the first one. These must be tied as tightly as possible, to prevent possible leakage of the gomenol from the gauze. The flexi-tissue is severed  $\frac{1}{2}$  inch distal to the ties, leaving the sack with a short stump which is pushed inside the chest wall beneath the rib above the chest wall opening. The muscles are approximated in layers; the fascia and skin is closed without drainage.

For the closure of a residual cavity following thoracoplasty, an approach is made to the extrafascial plane over the cavity, either by removal of regenerated bone sufficient to permit stripping, or, in case of a partial thoracoplasty, with a cavity remaining near the last resected rib, it is preferable to resect a portion of the rib and enter the extrapleural space as in a primary procedure. The technic otherwise is the same.

The pre- and postoperative care is the same as for any major chest operation. The wound is inspected in 48 hours and the dressings changed. The skin sutures are removed on the fifth to seventh postoperative day.

**Complications** — The postoperative reaction is usually mild. There is no shock. There is usually a postoperative temperature lasting a week and some exudate formation in the majority of cases, but it is usually benign and absorbs spontaneously; if massive, and causing further stripping of the lung from the chest wall, it must be aspirated. If aspiration is not followed by reexpansion of the unnecessarily stripped lung, the pack should be removed and the space converted into an extrapleural pneumothorax. This accident has been of rare occurrence. Should the fluid become infected, the extrapleural space is irrigated with *Dakin's solution* or *azochloramid*.

The pack is allowed to remain as long as possible, depending upon the underlying pathology. One patient in the writer's series is ambulant with a pack in position now over 4 years. She has no complaints.

The pack is removed under local anesthesia through a small incision. The approach is through the rib bed entered at the time the pack was introduced. Once the pack is visualized, an incision is made through the sack near the neck, a crochet hook is introduced into the sack and the loop of decnatol is fished for, or, if it cannot readily be found, a piece of gauze is hooked and drawn through the opening of the sack, whence the entire strip of gauze is pulled out, after which the sack is pulled through the wound. If no bronchus communication exists, the space is irrigated with normal saline solution and closed without drainage.

The extrapleural space conducts itself like an extrapleural pneumothorax—either the lung slowly expands or fills with exudate which may or may not require aspiration or conversion into an



extrapleural pneumothorax or oleothorax.

**Advantages**—The advantage of the operation over extrapleural pneumothorax is that the collapse is selective, and refills with air or oil are not required. The period of hospitalization is short and patients may return to their homes even if remotely located, as there is no occasion to report for refills. The operation has all the advantages of partial thoracoplasty. It, however, is not shocking and may be done on poor surgical risk cases unsuited for thoracoplasty.

**Anesthesia**—Because of the advantages of controlling bleeding with the high frequency current, *nitrous oxide* is used for general anesthesia preceded by *nembutal*,  $1\frac{1}{2}$  grains (0.1 Gm.), three-quarters of an hour before operation, and *avertin*  $\frac{1}{10}$  to  $\frac{1}{9}$  grain (60 to 70 mg.) per  $2\frac{1}{5}$  pounds (1 kg.) of body weight is instilled into the rectum 20 minutes before surgery.

**Preparation of Gomenol Gauze**—The 1 per cent oil of gomenol gauze is prepared as follows: A 10-yard strip of 2-inch gauze bandage is unrolled and loosely packed in the bottom of a 1-pint Mason fruit jar. To the end of this gauze strip a 10-yard section of 2-inch bandage, which has been unrolled and soaked with 1 per cent gomenol and wrung dry as possible, is then tied with decnatol to the first strip of gauze placed in the jar. After the end of the second strip has been reached, a third strip of dry gauze is tied to the gomenol gauze and the 3 lengths lightly packed into the jar. The jar is capped loosely and autoclaved for 20 minutes at 20 pounds pressure. It is rotated, after removal from the autoclave, so that the oil is evenly distributed through the gauze.

### Artificial Pneumoperitoneum

Artificial pneumoperitoneum has been used as a therapeutic or diagnostic procedure for many years. As early as 1895 the introduction of air into the peritoneal cavity was used in the treat-

ment of tuberculous peritonitis with ascites. Some years later its use was extended to the treatment of tuberculous enterocolitis without peritoneal involvement.

A number of things suggested the use of artificial pneumoperitoneum for pulmonary disease. Upward pressure on the diaphragm has been considered a factor in the retrogression of pulmonary lesions of pregnant tuberculous women, such as is commonly observed during the latter months of gestation. Accidental pneumoperitoneum occurring during an intended pneumothorax insufflation and the improvement of pulmonary lesions in patients receiving pneumoperitoneum for a complicating tuberculous enterocolitis led Banyai to suggest this as a useful collapse procedure to be added to the armamentarium of tuberculosis therapy. Vajda, in 1933, reported 2 cases; one in which an injection of 1200 cc. of air raised the diaphragm, lessened its excursion and resulted in symptomatic improvement of the patient; another in which 700 cc. appeared to control protracted hemoptysis. He suggested pneumoperitoneum as a useful adjunct in the treatment of bilateral pulmonary tuberculosis. Recognizing its limitations, artificial pneumoperitoneum is now accepted by many as the most rational form of therapy for certain patients in whom pneumothorax has failed or phrenic nerve block alone is inadequate.

By elevating the diaphragm, pneumoperitoneum relaxes the lung and reduces its volume. Banyai<sup>25</sup> has shown that the roentgenologic surface area of the lung can be reduced by an average of 10 to 15 per cent with pneumoperitoneum, appreciably more than with a phrenic nerve block alone. Assuming that the decrease in roentgenologic surface area reflects the degree of pulmonary relaxa-

tion and that relaxation of the tuberculous lung is the most important treatment factor he concludes<sup>26</sup> that pneumoperitoneum is superior to phrenic nerve block in the treatment of pulmonary tuberculosis. He further points out that pneumoperitoneum has the following advantages over phrenic nerve block:

1. Pneumoperitoneum is a reversible, adaptable procedure which may be discontinued at any time.

2. It relaxes the lung gradually.

3. Relaxation of the "good" lung, with consequent hyperemia, creates an unfavorable site for the development of metastatic tuberculous foci from the "bad" lung.

4. By elevating and supporting the diaphragm pneumoperitoneum makes coughing easier, more efficient and more productive.

5. Pneumoperitoneum is useful in bilateral tuberculosis whereas a bilateral phrenic is neither accepted nor feasible.

6. Because of its beneficial effect on a complicating tuberculous enterocolitis, pneumoperitoneum may improve ingestion, digestion and the general condition of the patient, resulting in an increased immunity, resistance and capacity for repair of the pulmonary lesions.

**Indications**—It is practically impossible to state specific indications for the use of a pneumoperitoneum in the treatment of pulmonary tuberculosis. Its use must depend largely on the physician's experience with this and other forms of collapse therapy. Generally speaking, it is suggested for patients in whom pneumothorax has failed and whose pulmonary lesions are not so extensive as to demand the more formidable procedures of surgical collapse. Trimble and Wardrip<sup>27</sup> consider that it has particular value in patients with fairly extensive bilateral pulmonary tuberculosis who neither can be given pneumothorax because of adhesions, nor can tolerate more drastic procedures of collapse therapy; also as an adjunct in obtaining a greater rise of the paralyzed hemidiaphragm. In preponderantly unilateral

disease, pneumoperitoneum is logically used in conjunction with phrenic nerve block in order that greater selective relaxation of the more diseased lung can be attained.

Pneumoperitoneum must also be kept in mind as a possible method for controlling hemoptysis<sup>28</sup> and as a preliminary measure to improve the general condition of a patient who would otherwise be unable safely to undergo the more extensive surgery indicated.<sup>29</sup>

**Complications**—Serious complications of well-performed pneumoperitoneum are practically negligible. Possible complications include hernia, pain, subcutaneous emphysema, abdominal distention (meteorism, effusion), peritoneal adhesions, obliterative peritonitis and<sup>30</sup> mediastinal emphysema. Severe cramps may occur if the treatment is given during a menstrual period. If the procedure is properly performed there should be no danger of puncturing the intestine or other viscera. Burge<sup>31</sup> states that he has never seen pneumoperitoneum increase dyspnea. On the other hand, the dyspnea of a complicating emphysema is said to be relieved.<sup>32</sup>

**Technic**—The technic is not difficult to master. A point on the anterior abdominal wall or in the subphrenic area is anesthetized with *novocain*. A small-gauge infiltration needle may be used for anesthetization of the peritoneum. For the injection of air an ordinary pneumothorax needle, 19- or 20-gauge, is very satisfactory. The writer has found it very useful to keep the hilt of the needle filled with novocain while inserting it. As soon as the needle penetrates the peritoneum, the solution will fall away from the hilt. The needle is then connected to a pneumothorax apparatus with manometer. Ordinarily there will be no manometric pressure readings<sup>33, 34</sup> until a considerable amount of air has been introduced, unless the subphrenic approach has been used. The air is allowed to flow slowly through the needle. If high positive pressures follow the injection of a small amount of air, in the absence of peritoneal adhesions, the needle

probably has not penetrated the abdominal wall. If the point of the needle is in the peritoneal cavity, the air will flow freely. Weekly injections of 500 to 1500 cc. of air can be made and the progress of the treatment must be carefully followed by fluoroscopic examinations. Oxygen is often used in place of air for the early treatments and in the presence of complicating enterocolitis<sup>31</sup>

Early treatments are usually accompanied by pain in the shoulder and sometimes by abdominal discomfort. The signs of pneumoperitoneum (absent liver dullness, shifting tympany) should, of course, be present.

**Results**—The results of artificial pneumoperitoneum therapy will depend largely on proper selection of patients. In reviewing 200 cases treated with pneumoperitoneum at Olive View Sanatorium, Bennett<sup>35</sup> reports sputum conversion in 57 of the 173 in whom it had been positive and cavity closure in about 28 per cent of 211 cavities. The consensus of those physicians who have had considerable experience with artificial pneumoperitoneum is that its use, in selected cases, has improved the results of tuberculosis therapy.

### Transparietal Cavity Drainage

While the open drainage of pyogenic lung abscesses is now the treatment of choice, the use of this method in tuberculosis has met with but sporadic success. This is in large part due to the chronicity of the disease itself permitting a long-standing bronchocutaneous fistula to interfere with the normal physiology of the remainder of the lung. Bronchopneumonia is a frequent result.

In 1938, Monaldi<sup>36</sup> reported excellent, immediate results following the intubation of tuberculous cavities through the chest wall in cases with complete or incomplete bronchial stenosis. Intermittent suction of varying degrees was applied to a graduated catheter inserted

into the depths of the cavity. Closure occurred by both contracture of the cavern wall and aeration of the surrounding atelectatic tissue.

As Kupa<sup>37</sup> mentions, suction aspiration is not a substitute for thoracoplasty but has a definite value when contraindications to major surgery are present, such as tracheobronchial disease, low vital capacity, and contralateral disease. It is essential that the pleural surfaces are firmly adherent, in order to avoid spontaneous pneumothorax and empyema.

The procedure is carried out under the fluoroscope, and after determining the exact depth from the skin, a graduated trocar is introduced through which a graduated catheter, 12- to 16-gauge, is inserted into the cavity. The trocar is withdrawn and the catheter clamped off and fixed to the skin. In 24 hours, gentle suction is applied to the catheter to clear it of secretions and, unless there has been considerable hemorrhage, a suction device is attached at this time. Secretions are collected by a trap introduced between the suction apparatus and the catheter, and from -5 to -25 cm. of water pressure applied. Usually suction is maintained only during the day, but in large rapidly secreting cavities it may be necessary to maintain it continuously. The catheter is clamped off in the intervals when it is not being used.

Thick secretions which frequently block the catheter during the first few days of treatment gradually become thinner and in several weeks begin to diminish in amount, accompanied by a corresponding change in character and volume of the sputum.

While closed or partially closed cavities are more apt to yield to this method of treatment than open ones, thin-walled cavities with adequately patent bronchi frequently close, especially if they are surrounded by relatively normal lung tissue. Here the orifice of the catheter should be the same or greater in diameter than the draining bronchus if optimum pressure relationships are to be maintained within the cavity.

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## SYPHILOLOGY

By CARROLL SPAULDING WRIGHT, B S., M.D.

**Diagnosis—Serologic Tests for Syphilis**—There are numerous questions that arise in connection with serologic tests. In a discussion of "Laboratory Problems in the Study of Syphilis," Eagle<sup>1</sup> states that a physician who must interpret laboratory reports may well ask "what is the significance of a persistently positive test of a person being treated for syphilis?" Does it reflect persistent infection, with the continued elaboration of a reactive substance? Or may a positive serum reaction be present for months and many years after the actual infection has been completely eradicated and be

of no more diagnostic or prognostic significance than a Widal reaction persisting after recovery from typhoid fever? Further work is needed to determine the significance of a positive test for syphilis in a patient with tuberculosis, trypanosomiasis, serum-treated pneumonia, infectious jaundice, and many other conditions reputed to cause false positive reactions, but for which the evidence is nonconclusive. Eagle feels that it is inconceivable that the painful, expensive and prolonged administration of the arsphenamines and bismuth compounds, with the undesirable and rather frequent

toxic effects which often follow their administration, could constitute the last word in the treatment of syphilis. (The 5-day treatment seems to be a step towards the solution of this problem.)

"How do the officially recognized serologic tests for syphilis rank in specificity and sensitivity?" In answer to this question Nagle<sup>2</sup> states that since 1935 the United States Public Health Service has conducted 4 surveys for the appraisal of the specificity and sensitivity of various serologic tests for syphilis. As a result of these surveys, six tests were selected as being outstanding in accuracy, and were approved for use in the serologic diagnosis of syphilis. These 6 tests included 4 precipitation methods (Kahn, Kline, Eagle and Hinton) and 2 complement-fixation methods (Kolmer and Eagle).

In the 4 surveys over 1200 nonsyphilitic control cases and 1000 syphilitic cases were examined by the authors of the various tests in their respective laboratories. It may be assumed that the results obtained by these serologists represent the highest possible attainment with their respective tests. At the present time, when so much emphasis is being placed on the control of syphilis, a summary of the work done by these men should be valuable as a guide to laboratory directors in the choice of a routine test to be used in their own laboratories.

There is a difference in the specificity of the 6 serologic tests which the American evaluation committee considers as "reliable." In the same number of nonsyphilitic sera (about 1200), 1 test gives 1 positive and 5 doubtful reactions and another, 12 positives and 31 doubtful reactions. The high specificity obtained by the Kahn and Kline tests should influence the United States Public Health Service Committee to modify their recommendations: "An efficient serodiag-

nostic test for syphilis should possess specificity of 100 per cent. Any test which yields even 1 per cent of false positive reactions should be so modified as to increase its specificity, even with some slight sacrifice of sensitivity." They could now recommend a higher and more definite standard of specificity.

Of the 6 officially recognized tests, it was found that the standard Kahn test possesses the greatest specificity. Kahn examined 1983 nonsyphilitic control cases (blood serum) in the 4 surveys under discussion and in 3 previous official surveys, and yielded only 1 false positive reaction. The Kline diagnostic test ranks second, yielding 2 false positive reactions in 1201 control cases. The Eagle complement-fixation test ranks third, yielding 1 false positive in 613 control cases. The Kolmer test ranks fourth, yielding 3 false positives in 1203 control cases. The Eagle precipitation test ranks fifth, yielding 6 false positive reactions in 1082 control cases. The Hinton test ranks last in specificity, yielding 12 false positive reactions in 1188 control cases. In regard to sensitivity, the Hinton test ranks first; the Eagle precipitation test, second; the Kline diagnostic test, third; the standard Kahn test, fourth; the Eagle complement-fixation test, fifth; and the Kolmer test, last.

Although the Kahn presumptive and the Kline exclusion tests are not "officially recognized," both showed such high specificity and sensitivity that they compare favorably with the 6 tests recognized by the United States Public Health Service as "reliable." The Kahn presumptive test yielded only 1 false positive reaction in 637 nonsyphilitic control cases and was found to be more specific but less sensitive than the Hinton test and slightly more specific but definitely more sensitive than the Eagle

precipitation test. The Kline exclusion test yielded 5 false positive reactions in 625 controls and was found to be more sensitive than either the Hinton or Eagle precipitation test but less specific.

**Provocative Wassermann Test** — Gennerich called attention to the phenomenon, occasionally occurring, of a negative complement-fixation reaction becoming positive after the intravenous injection of a small dose of arsphenamine and of the value of this "provocative Wassermann," as he called it, in the diagnosis of obscure syphilitic infections and as an aid in the determination of whether or not a patient has been really cured of the infection, Milian, Herxheimer and Michaelis reported similar observations. Its value as a diagnostic aid and guide to therapeutics appeared to be established.

Since then, further observations on this phenomenon have been published, both acclaiming and declaiming Gennerich's observation, its interpretation and value in the study of syphilis. Pease accepted the phenomenon of provocatory stimulation and considered it a serologic Jarisch-Herxheimer reaction, the most probable explanation in view of present knowledge; whereas King, who did not even think that there was such a phenomenon, came to the conclusion that the positive result which sometimes follows an injection of arsphenamine is due either to normal variations in the amount of reagin present in the blood, as shown by Craig, Thaysen, and others, or to variations in technic or the reagents used in the performance of the complement-fixation tests on different days. The observations of Boas appeared to favor this latter assumption, based upon a lack of sufficient standardization of the complement-fixation test, since he was able to obtain different results using the same serum, the same technic and the same

reagents, but at different times. Furthermore, despite the fact that Craig attributed the fluctuations in degree of complement-fixation to changes in the actual amount of reagin in the blood, the question necessarily arises whether or not such changes may not result from slight variations in the test itself. Thus, Haller has shown that the factor in the blood producing positive complement-fixation is a practically constant element, indicating that the fluctuations observed by Craig and others were probably due to variations in the test as performed from day to day. The value of the standardized technic becomes evident.

After a study of 150 cases, Pollitzer concluded that the provocative test is a useless and often a misleading procedure, largely because positive complement-fixation reactions may be found months after a provocative test. This, however, does not appear to be a valid reason for discarding a test from which immediate information concerning an infection such as syphilis may be obtained in a fairly large percentage of the studies. It has never been maintained that a negative "provocative" indicates the absence of syphilis. Furthermore, although not always positive in the presence of known and even active clinical syphilis, at the present time the complement-fixation test is considered a measure of spirochetic activity; whether it be after a provocative test or months after such a test, it must be considered in the same light.

The observations of Nichols, in which he used the luetin test to control the positive provocatory reactions, are interesting in that the positive "luetins" corresponded exactly with the positive "provocatives." Considerable doubt, however, has been cast upon the actual value of the luetin test itself by the work of Stokes, of Alderson, and of Kolmer and Greenbaum. The studies of these

last authors do not, of course, contradict the fact that there is such a phenomenon as provocatory stimulation of a syphilitic process, nor do they minimize the value of the provocative test, since many observers, in particular Stokes and O'Leary, and Craig, found that the phenomenon not only actually occurs, but has definite value, the amount of which varies with the author. By the use of various technics, the average percentage

by an increase in the titer of the blood Wassermann—the so-called “provocative phenomenon.” This increase supposedly reaches its maximum between the fifth and tenth days, after which the titer subsides promptly to or below its original level. If quantitative Wassermann titrations are performed, the provocative effect may be observed almost uniformly at the start of treatment in early syphilis, less frequently in late syphilis (Moore).

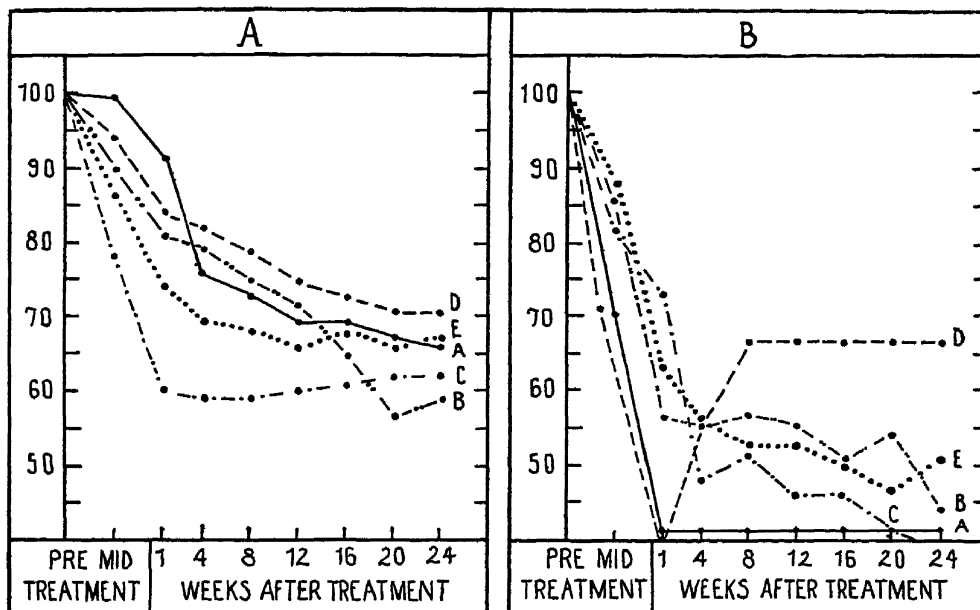


Fig. 1 — Fall in titer of Wassermann antibody following various types of chemotherapy. A, Acquired syphilis; B, congenital syphilis (A, arsphenamine or neoarsphenamine; B, sulfarsphenamine, C, arsphenamine and mercury, D, mercury; E, bismuth) (Belding. Am J. Syph., Gonorr. and Ven. Dis.)

of positives obtained by these authors and by Sheperdson was  $18\frac{1}{3}$  per cent.

An interesting and disturbing factor appeared to have been added to the significance of the provocative test by the observations of Strickler, Munson and Sidlick, *i. e.*, that the positive reaction is due to the arsenical. The studies of Kolmer, of Kilduffe and of Boas and Kissmeyer do not, however, confirm these observations.

It has in the past been held that both in early and late syphilis the first injection of an arsphenamine may be followed

The *provocative procedure*, therefore, consists in administering 5 grains (0.3 Gm.) of arsphenamine (or 70 grains—4.5 Gm.—of neoarsphenamine) intravenously followed by 7 daily Wassermann tests beginning the third day after the injection. Greenbaum and Wright using the Kolmer Wassermann technic observed an increase of positive reactions on approximately 17 per cent of cases.

A provocative effect has also been observed on the spinal fluid.

The provocative Wassermann should never be employed as a criterion of cure.

**Effect of Antisyphilitic Drugs Upon Wassermann Reaction**—The results of quantitative studies of the Wassermann reaction on 178 patients with acquired syphilis and 55 patients with congenital syphilis during and after treatment with arsphenamine, neoarsphenamine, sulfarsphenamine, bismuth mercury, and arsphenamine and mercury combined, are presented by Belding.<sup>3</sup> The author's charts graphically show the effects of these drugs upon the titer of Wassermann antibody and since there is no indication of a temporary stimulation of titer, Belding's charts tend to cast doubt upon previous ideas as to the provocative Wassermann test.

The reduction of the Wassermann antibody titer was recorded quantitatively during and after treatment in 233 syphilitic patients who were given various preparations of arsphenamine, mercury, and bismuth. By the selection of groups of patients balanced as to clinical type, previous treatment, duration of the disease, and strength of the Wassermann antibody, and by the use of a quantitative technic, it was possible to eliminate many of the factors which modify the action of drugs on the Wassermann reaction.

In the patients with late acquired syphilis an average reduction of the Wassermann antibody titer of 37 per cent was obtained with all the drugs except mercury (used alone), which gave 29 per cent. No significant difference was noted between neoarsphenamine, sulfarsphenamine, and arsphenamine. Combined treatment with arsphenamine and mercury gave results which were only slightly better than with arsphenamine alone.

The patients with congenital syphilis gave a reduction of 54 per cent. The greater response is in part explained by the intensity of treatment.

The reduction in the Wassermann antibody titer was permanent up to 24 weeks after treatment.

The rate of serologic reduction was fairly uniform for all the drugs and reached a maximum at about the twelfth week after treatment.

Under arsphenamine therapy the serologic reduction in early syphilis was nearly twice that in late syphilis and the response was more rapid.

In the patients with acquired syphilis no difference in respect to clinical type was observed, except for a lower response in patients with cerebrospinal syphilis. Bismuth gave the best serologic results in cerebrospinal syphilis.

**Infectiousness of Syphilis**—According to O'Leary and Williams,<sup>4</sup> it has been the impression that the ability of persons with syphilis to transmit the disease tends to vanish by the fifth year of the infection. This impression is based on the observation that when the period between acquiring the disease and marriage was longer than 5 years, it was rare that the normal marital partner became infected.

Seeking information on this important point, therefore, these authors present the results of analysis of 1175 married couples, at least 1 partner of each couple having syphilis. From a study of this material, with particular reference to the time relationships of the first infection with regard to whether the second partner acquired the disease, the authors conclude:

"Syphilis may be considered to be infectious during the first 5 years the patient has the disease, but each year thereafter the possibility of such a patient's transmitting the disease decreases with each year until it approaches a vanishing point by the tenth year. An accurate study of the value of arsphenamine and bismuth in preventing spread of the dis-



ease was not possible during the present study because few patients concerned were administered what would today be called adequate treatment. Among those who did receive some treatment before marriage, the incidence of infection in the marital partner was found to be less than when no treatment whatsoever was administered. Information was obtained tending to confirm the viewpoint that the disease is infectious during the early phases and only slightly infectious in the late phases of the disease, as evidenced by the fact that less than 1 per cent of the patients who had early syphilis had a partner who at the time of examination manifested signs of late syphilis."

**Treatment—Long-term Results in Treatment of Early Syphilis**—In discussing a treatment plan and the outlook for "cure" in a patient in whom the diagnosis of early syphilis has just been made, it is advantageous for the physician to be able to give definite statistics on past results of the proposed therapy. In a survey of the literature, Padgett<sup>5</sup> found no satisfactory long-term evaluation of the results of attempts to treat patients with early syphilis by modern methods. He therefore analyzes the results of treatment of 551 patients who were treated for early syphilis and then completely re-examined 5 or more years after the termination of their original treatment. The period of post-treatment observation was more than 5 but less than 10 years (mean 7.6 years) in 278 patients, and it was more than 10 years (mean 14 years) in 273 patients. The mean period of observation was 10.8 years for the group as a whole.

The material of this study cannot be considered a random sample because there were more colored women (at the expense of men of both races) than was typical for the clinic from which the patients were drawn. The effort was made

to nullify this objection by carefully defining all collateral and conditioning factors.

Comparison of the results of examination at approximately 5 years and at 10 or more years after the original treatment for early syphilis in the 268 patients on whom such comparative examinations were made, revealed no patient with a less satisfactory result at the latter examination than at the former. The author considers this fact to be of crucial importance.

Analysis of the final outcome by race and sex revealed no significant difference in the incidence of "cure." Among those who did not achieve "cure," however, neurosyphilis was  $2\frac{1}{2}$  times as frequent among the whites. The negroes of the group had cardiovascular syphilis more often, but the majority of the unsatisfactory results observed in these patients consisted of the persistence of a positive serologic test for syphilis in the blood without other manifestations of the disease. Neurosyphilis was also  $2\frac{1}{2}$  times as common among the men as among the women who were not "cured."

Elevation of the blood-pressure did not prejudice the prospects of attaining "cure" for the 53 patients who sometimes or always were found to have a systolic pressure about 145 mm. of mercury. The presence of abnormalities in the cerebrospinal fluid was found to reduce greatly the percentage of "cures" attained, and the reduction was in proportion to the severity of the abnormalities.

Among the 534 patients treated, the best results were observed among those who began treatment during the seronegative primary stage, of whom 82 per cent achieved "cure." The worst results, only 55 per cent of cures, were seen among patients whose treatment was begun in the seropositive primary stage.

Among patients with secondary syphilis when treatment began, 68.8 per cent were "cured" and in those with early latent syphilis, 58.7 per cent were "cured." These differences are, according to the author, probably to be explained on the basis of the immune reaction of the host to the parasite and its disruption by treatment. Emphasis is placed on the fact that while the incidence of "cure" was higher in the patients who came under treatment with secondary syphilis than among those in the early latent group, the incidence of a persistently positive serologic test for syphilis without other evidence of the disease was more than twice as great in the latter as in the former. Neurosyphilis was more than twice as common among those who began treatment with seropositive primary syphilis as among others, and it accounted entirely for the increased incidence of unsatisfactory results in this group.

The best results were observed in the patients who began treatment with syphilis of less than 1 month's duration, while the worst results were seen in those whose treatment began during the second month of the disease.

The development of early or intermediate relapse was found to be of grave prognostic significance. "Cure" was nearly 3 times as common among those who were not observed to relapse as in those who were, and neurosyphilis was approximately 6 times as common among the latter.

"Cure" was attained by 83.4 per cent of the patients whose treatment during the first 6 months was by a continuous system, and this increased to 90.4 per cent if treatment during the second 6 months was likewise continuous.

This was in sharp contrast to intermittent and irregular treatment, of which the former was approximately equal to

no treatment at all (35.3 per cent spontaneous "cure") and the latter was no better. In view of this and other considerations, the author raises the question as to whether, if the patient will not co-operate to receive regular treatment, it would not be better to give no treatment at all rather than irregular or intermittent treatment.

Patients who were given 7 to 9 injections of arsphenamine during the first 3 months did as well as those who had twice as much treatment scattered over the first 2 years.

The results of this study indicate that serologic testing is not sufficient to determine the true status of patients who were treated for early syphilis in the past, and that complete and painstaking periodic physical examination is likewise essential.

For practical purposes, a patient who has done well for 5 years following the termination of treatment for early syphilis, and at that time has no signs of the disease, may be discharged from further observation.

**Massive Arsenotherapy in Early Syphilis by Continuous Intravenous Drip Method**—On April 12, 1940, a meeting was called in order to review the results of massive dose chemotherapy of syphilis by means of the intravenous drip. The observations reported represented an experience with more than 375 male patients with the primary or secondary stage of syphilis.

The preliminary work with arsphenamine was first discussed by Baehr.<sup>6</sup>

Rapid sterilization of the body by massive arsenotherapy was the primary aim of Paul Ehrlich. Later, others also attempted to administer amounts of Ehrlich's chemotherapeutic agent comparable to those which are being reported today, but the dangers involved made it necessary to revert to small divided

doses given intravenously every 5 days for 1 to 2 years. This prolonged method of therapy results in a loss of 40 to 80 per cent of clinic patients while they are still in the communicable stage of the disease and can continue to transmit their infection to others. The disease therefore has continued to spread annually to several hundred thousand persons in this country, despite the availability of a specific remedy for 30 years.

In 1931, Hirshfeld, Hyman and Wanger, working in the laboratories of the Department of Pharmacology, Columbia University College of Physicians and Surgeons, under Prof. C. C. Lieb, described the syndrome of "*speed shock*" in laboratory animals following rapid intravenous injections. The work suggested that the reactions following intravenous administration of many therapeutic substances, which are called nitritoid crises, anaphylactoid reactions and hemoclastic or colloidoclastic disturbances, might in fact be "*speed shock*" and might represent a manifestation of a technical error rather than a specific pharmacologic effect of the injected chemical. It was demonstrated by these authors that "*speed shock*" could be prevented by an intravenous drip velocity which could be regulated so that fluids were introduced into the body at a rate of approximately 2 or 3 cc (60 to 90 drops) per minute. It was also observed that this slow rate of flow also permitted the introduction of remarkably large amounts of highly toxic substances, such as anaphylatoxin, histamine and even heavy metals, with complete impunity.

In 1932, Louis Chargin, syphilologist of the Mount Sinai Hospital and the New York City Department of Health, proposed that the slow drip method might permit the introduction of large amounts of an arsphenamine in the treatment of syphilis. With the authorization

of the Trustees of the Mount Sinai Hospital, this work was begun at this institution.

In the first series, 25 patients suffering from recently acquired syphilis were treated by Chargin, Leifer and Hyman. Sixty to seventy grains (4.0 to 4.5 Gm.) of *neoarsphenamine* were administered in 5 days, an amount equal to that ordinarily given in 3 months. No other form of therapy was used, the patients being followed periodically during the succeeding years. At the end of 5 years, 15 of the 25 persons in the original group were still under observation. Twelve had remained well and their blood and spinal fluid had given negative serologic reactions for more than 5 years. These 12 and the following patient therefore he declared to have been cured.

One man became reinfected after having had completely negative Wassermann reactions of the blood and spinal fluid for 3 years and 2 months. Fortunately, he reported promptly when the new primary lesion was still in the seronegative stage. The lesion had appeared after the proper incubation period following exposure to a woman who was found to have an active infection. It was at a new site on the penis and spirochetes were easily demonstrable by the dark-field method. Treatment was postponed until after the Wassermann reaction had become positive under observation and after a typical secondary rash had appeared. There is therefore no question that this condition was a reinfection, which constitutes unequivocal evidence that the 5-day treatment 3 years before had effected a complete cure.

Another man had a similar experience 1 year and 7 months after treatment and apparent cure, but because of the shorter time interval the writer and his colleagues have labeled this case a possible failure. The fifteenth member of the

group, a hospital orderly, who had insisted on administering a bismuth compound to himself, gave a history of having had a 2 plus reaction in the blood on 1 occasion, although both the blood and the spinal fluid reacted negatively during observations before and after that time. His case was also counted as a possible failure.

It was tentatively concluded that permanent and complete cure was possible with 5 days' treatment and that this technic might provide the means for the more rapid eradication of the communicable stage of syphilis. The observations, if confirmed, offered a new vista for the control of syphilis, but caution was advised until a larger experience had demonstrated its safety.

Under the careful control of a committee, the original investigators treated a second group of 86 patients with *neoarsphenamine*. The observations on the first series, treated in 1933, were confirmed. As reported before the American Medical Association in 1939 and before the Association of American Physicians, about 86 per cent of the patients who continued under observation after the 5-day course of treatment remained clinically well, with negative serologic reactions of both blood and spinal fluid.

After this report was published, the serologic reactions became completely negative in 4 cases in which results were still pending, and these cases therefore may be added to the group with satisfactory results. Of the 78 patients followed, 71 now have negative serologic reactions of the blood and the spinal fluid and are clinically well. The percentage of favorable results with neoarsphenamine is therefore 91 per cent.

Of the entire series of 86 patients to whom the treatment was given, 1 died and 7 disappeared from observation shortly after the treatment was con-

cluded. Of the 7 cases, 2 were never seen again after discharge from the hospital, 4 were lost after paying only 1 visit to the follow-up clinic 2 weeks after discharge, and 1 was seen for the last time 6 weeks after discharge, at which time the Wassermann reaction of the blood was fading rapidly. If all 7 patients who were lost shortly after completing treatment are regarded as possible failures, an unwarranted assumption, it would reduce the percentage of favorable results to 83 per cent. As all 7 patients had completed the full course of treatment, however, it is reasonable to assume that the percentage of favorable results is equal to that of the group of 78 that were followed.

Toxic phenomena, chiefly polyneuritis, frequently followed the use of neoarsphenamine. Although usually mild, they were sufficiently disturbing to warrant the trial of another, less toxic arsenical. In the fall of 1938, after the only treatment fatality in the 2 series of 111 patients treated with neoarsphenamine (cause of death, hemorrhagic encephalitis), further work with this arsenical was discontinued and *mapharsen* was substituted.

The use of mapharsen was begun in October, 1938. About 265 patients have now been treated with this preparation.

*Technic*—The technic of intravenous drip as described by Leifer<sup>7</sup>:

The apparatus employed is packed and autoclaved in a special container, devised by Joseph Turner, Director of the Mount Sinai Hospital. The feature of this box is a slot containing perforations which are open while in the autoclave and closed at all other times to prevent contamination.

Each set consists of a gravity flask and 2 lengths of translucent rubber tubing connected by a Murphy drip. The longer strip of tubing is attached to the gravity flask; the shorter, to an adaptor which

fits a standard 20-gauge, 1½-inch (3.8 cm.) needle.

The drugs are dissolved in a solution of triple-distilled water containing 5 per cent dextrose. Because of instability, the neoarsphenamine solutions were made up at hourly intervals, as has been previously described. In the present work, the content of an ampoule containing 1 grain (60 mg.) of mapharsen has been dissolved in 600 cc. of the diluent. Where facilities are not available for the preparation and sterilization of solutions, commercial sets of the type approved by the Council of Pharmacy of the American Medical Association may be purchased ready for use. Bernard I. Kaplan, internist at Sing Sing Prison, has employed the latter technic, simply adding the drug to the commercial set. The solution of mapharsen is stable. At present 4 doses of the drug in the diluent are given without intermission each day, so that each patient receives 3¾ grains (240 mg.) of mapharsen in 2400 cc. of 5 per cent dextrose solution, which contains 4 ounces (120 Gm.) of the sugar. The rate of flow is approximately 3 cc. a minute. Ordinarily the drip is set up about 8 A. M. and the full dose has been injected by the end of 10 to 12 hours. At the end of this period the needle is withdrawn, treatment being discontinued during the night but resumed the next morning. This procedure is carried out daily for 5 consecutive days until a total of 18 grains (1200 mg.) of the drug has been administered in 12,000 cc. of diluent, containing 20 ounces (600 Gm.) of dextrose. The total arsenic content is approximately 6 grains (360 mg.).

The choice of the vein is an important consideration. In the earlier work, in 1933, the site of injection was the cubital fossa. This required splinting of the arm, which not only interfered with the care of the patient but was uncomfort-

able, the pressure of the splint occasionally leading to traumatic neuritis. Throughout the recent work, the elected site for the insertion of the needle has been a vein on the forearm between the elbow and the wrist. This permits free movement of the elbow, and no splint is required; the patient may assist in feeding and in nursing procedures, such as the use of the bedpan; there is less danger of dislodging the needle from this site than at the bend of the elbow, where motion occurs. It is desirable to insert the full length of the needle, up to the hub, for firmer anchorage. The right and the left arm are used alternately for the injection procedure. Usually a vein can be employed again after a rest of 24 hours.

Local disturbances are infrequent. It was thought that the slow injection of mapharsen would cause pain in the arm, but this rarely has been encountered. Infiltrations have occurred, but with the greatest rarity—in less than 0.5 per cent of the patients treated. Traumatic neuritis has been absent since the discontinuance of the use of arm splints. Local infection has never been seen.

The nursing problem during the period of treatment consists of the preparation of fresh solution for each patient at the end of 2 or 3 hours and the refilling of the gravity flask. Meals are served on the ordinary bed tray. Patients can feed themselves. They are also capable of handling the urinal but, naturally, must be assisted somewhat in the use of the bedpan. The latter disturbance may be prevented by having the patient evacuate or have an enema during the evening, when treatment has been discontinued.

The patients are given a high calory diet, rich in starches and carbohydrates. The majority of the patients read, listen to the radio or play cards during the

day. In the evening, after discontinuance of therapy, they may get out of bed. They suffer little or no discomfort. Many of them register a gain in weight of as much as 10 pounds (4.5 kg). This gain in weight is not due to any appreciable edema but may be explained by the fact that most of these patients, otherwise undernourished, are so well treated with regard to food and nursing care.

The routine examinations consist of the following:

1. Daily urinalysis, including determination of urobilin.

2. Determinations of the urea nitrogen content of the blood and icterus index at the beginning and at the termination of treatment.

3. Complete blood count, including that of the platelets, at the beginning and at the termination of treatment.

4. Complete physical examination on admission.

5. Serologic examinations made in 3 different laboratories (these include the Kolmer, Kline diagnostic, Kline exclusion, Kahn standard and titrated Wassermann tests).

6. Dark-field examination of material from all open sores.

7. Estimation of renal function by determination of the specific gravity of the urine.

8. Special tests of hepatic function by the bilirubin method.

9. Studies of the excretion of arsenic in the urine and in the stool and its concentration in the blood (these studies have been made on only a limited number of consecutive patients).

*Toxicologic Manifestations*—A report of the toxic manifestations observed in 270 patients treated with mapharsen in various dosages by the drip method of therapy was presented by Chargin.<sup>8</sup>

In the *neoarsphenamine* series, there was 1 fatality due to hemorrhagic encephalitis and a rather high incidence of polyneuritis (38 per cent). This led to the substitution for neoarsphenamine of another arsenical, namely, mapharsen, which then was efficacious therapeutically, judging by experience with a large series of patients with early syphilis treated by the routine method.

In the 270 patients for whom treatment with *mapharsen* was completed, there was no death due to the treatment. In 1 patient in the series hemorrhagic encephalitis developed. With this single exception there were no important toxicologic manifestations in any of the patients.

The primary or Herxheimer fever was also observed in the mapharsen series. This reaction consisted of a brisk rise in temperature on the first day of treatment. This febrile reaction has no serious connotation and does not interrupt the progress of the treatment. It was observed in 62 per cent of the patients receiving neoarsphenamine and in approximately 40 per cent of the present series.

Secondary fever, frequently associated with or followed by toxicoderma, appeared toward the latter part of therapy or after its termination. This occurred in 64 per cent of the neoarsphenamine series and in only 13 per cent of the mapharsen series. The secondary fever may appear without toxicoderma, and, similarly, toxicoderma may appear without febrile reaction. The toxicoderma is usually morbilliform, rarely urticarial. It occurred in 45 per cent of the neoarsphenamine series and in approximately 11 per cent of the present series. These eruptions should not be confused with the major dermatitides due to arsphenamine. They are not of serious import and do not sensitize the patients

to future injections of remedies of the arsphenamine group, since many of the patients who had toxicoderma have been treated again without any untoward cutaneous reactions.

Peripheral neuritis of a significant degree was not observed, although minor paresthesias, never significant, may occur after the patient's discharge from the hospital. It may be stated in passing that in the neoarsphenamine series the injection of thiamine chloride vitamin B<sub>1</sub> proved valueless as either a prophylactic or a therapeutic agent; also, the administration of vitamin C in preventing the secondary fever or the toxicodermas proved fruitless.

It is interesting to observe that the nitritoid reaction, which occurs in 0.1 to 0.5 per cent of all patients to whom injections of neoarsphenamine or arsphenamine are given, was not observed in a single patient in either series, almost 2000 injections of massive doses having now been given. The intravenous drip method has eliminated this reaction. This experience strongly suggests that the nitritoid crises and colloidoclastic and anaphylactoid phenomena are merely clinical manifestations of "speed shock," as first suggested by Hyman.

Renal function during treatment was carefully observed and studied. With the exception of transitory albuminuria in an occasional case, there was no evidence of any significant disturbance of renal function.

The effect of massive dose therapy with the arsenicals on the liver was studied. In addition to observations for clinical jaundice, daily examinations of urine for urobilin were made. The icteric index was followed, and special tests for bilirubin retention were performed by Louis Soffer and his associates. In this series there were 2 instances of transitory jaundice while the patients were in

the hospital. Occasionally a slight increase in the excretion of urobilin or in the icteric index was found later, but was transitory and, apparently, of no important significance. It was noted that in a number of instances the icteric index before treatment was found to be above normal, as high as 15. This may be considered indicative of mild hepatic damage due to syphilis. In most of these cases after the termination of treatment the icteric index fell to normal levels.

The effects of massive dose arsenotherapy on the hemopoietic system were observed. In the neoarsphenamine series there were 2 instances of thrombopenic purpura. The condition in 1 case was idiopathic and was cured by splenectomy; in the other, definite sensitivity to arsenic was found. In the series of patients treated by mapharsen no untoward effects on the formed elements of the blood were noted.

Cerebral complications and the major dermatitides remain the bugbear of arsenotherapy. In the neoarsphenamine series there were 2 instances of hemorrhagic encephalitis, 1 in which the condition proved fatal. In the mapharsen series, consisting of 288 courses of treatment, there were 3 persons with cerebral symptoms. Two of these had mild symptoms; 1 had a single convulsion and promptly recovered. Neither required active treatment. The third, a white man aged 25, was admitted with the diagnosis of seropositive primary syphilis. General examination revealed that he was suffering from chronic rheumatic cardiovascular disease affecting the aortic and mitral valves, but the process was inactive. He received 18 grains (1.2 Gm.) of mapharsen in 5 days. He took the treatment well. On the seventh day, *i. e.*, on the second day following completion of treatment, headache developed, and soon thereafter there was a convul-

sion, which was followed by 5 additional attacks in 4 hours. He lapsed into stupor for 48 hours. With repeated *lumbar puncture*, intravenous administration of a 50 per cent *solution of sucrose* and *paraldehyde* sedation, he completely recovered in 5 days and was in perfect condition 2 months after the episode.

*Public Health Aspects* — Massive arsenotherapy by continuous intravenous drip seems to offer new hope for the control of syphilis and merits significant consideration by public health officers as well as by clinicians, according to Rice.<sup>9</sup> Taking patients suffering from infectious syphilis "out of circulation," rendering a large portion of them permanently non-infectious and even curing a number of them add to the health of the community immeasurably. Prevention of the spread of this epidemic disease is thereby assured.

The advantages of this short period of treatment from the standpoint of cost seem obvious. The effects of this type of treatment in the management of latent and late syphilis are as yet undetermined, but here, again, the opportunity for improvement over present methods may indeed prove a boon.

The modern syphilis control program embodies elaborate and costly machinery for case finding and case holding. A great deal of this work will at 1 stroke be eliminated and made unnecessary by the ultimate perfection and universal application of this 5- or 6-day treatment with massive doses. When the fact is considered that even in well organized syphilis clinics the lapse rate is great—the co-operative clinic group reported that of 6807 patients with early syphilis, 5718 (84 per cent) had allowed treatment to lapse before receiving 20 injections of an arsenical drug—the actual and potential value of the massive dose

rapid therapy looms up as a genuine advance.

It should be possible with the first course of treatment to render permanently noninfectious at least 80 per cent of those infected with early syphilis, and it is conceivable that this figure may be even higher. The second course of treatment would clear virtually all of the remaining patients, with the exception of the irreducible minimal number of persons whose serum for some reason beyond present knowledge continues to give positive reactions.

The development and practical application of such a program would undoubtedly result in a tremendous saving in economy, in human suffering and disability, and in lives.

At this time it is particularly important to stress the applicability of massive dose chemotherapy to syphilis control in military forces. It would also result in tremendous savings in the treatment of migratory and transient groups which are an everpresent problem in certain sections of this country and even in a great city such as New York.

*Comment*—The presentation of the numerous papers which dealt very fully with all available data on the subject of "massive arsenotherapy" at the meeting called by the Commissioner of Health of the City of New York was followed by some very interesting discussions, some of which are very pertinent. C. W. Clarke pointed out that this method of treatment would not become available for some time to patients with syphilis throughout the country and that there is danger that a few physicians might undertake to administer treatment by the intravenous drip methods with disastrous results to their patients.

J. E. Moore, of Johns Hopkins Medical School, raised a number of timely and interesting points.



The patient's loss of time needs consideration. It was suggested that hospitalization for early syphilis is desirable. In Moore's opinion it is undesirable to take a patient with early syphilis away from his job and "out of circulation." It would seem much better from the standpoint of his morale and of his economic situation for him to stay at work if he can.

The risk of the method, of course, is an all-important consideration. The Reviewer is particularly impressed by the fact that, so far, in 374 patients treated there have been 4 examples of hemorrhagic encephalitis, of which 1 was fatal. The published and quoted data as to the incidence of hemorrhagic encephalitis with standard treatment methods are not accurate, at least so far as Baltimore is concerned. Among 30,000 patients with syphilis treated there, only 2 examples of hemorrhagic encephalitis have occurred. This is an incidence of 1 in 15,000 in place of an incidence of 1 in less than 100 here reported; and hemorrhagic encephalitis is one of the gravest complications of antisyphilitic treatment.

The therapeutic result of this method of treatment must, it seems to the writer, be measured not only against the results of the best form of standard treatment but also against the results of the poorest form. In other words, are the good results of the intravenous drip method superior to the results of 1 to 3 injections of an arsenical by the standard method? Not much is known about the results of poor standard treatment, but on the basis of 5- to 10-year follow-up of a large series of cases at the Johns Hopkins Hospital, they are about 65 per cent satisfactory, *i. e.*, 65 per cent of patients are "cured" both clinically and serologically by from only 1 to 3 standard injections of old arsphenamine. The results of massive arsenotherapy are perhaps

20 to 25 per cent better, but at an enormously increased cost to the community and increased risk to the patient.

Another point is whether the same result (and this, too, is best determined in the laboratory rather than in the clinic) might be accomplished by means of multiple divided doses instead of the continuous drip. May it not be possible to give the patient 2, 3, 4 or 5 divided doses within a given day or over a period of several days, with less inconvenience, equal safety and equally satisfactory results.

Much still remains to be done. It will be a number of years before results are available which justify the routine adoption of the system, and it ought not to be adopted in the meanwhile except as a research project.

***Scheme of Treatment for Pregnant Woman with Syphilis***—The United States Public Health Service has published an excellent pamphlet on "*Syphilis in Mother and Child*."<sup>10</sup> In outlining a scheme of treatment for syphilis in the pregnant woman, the following discussion is presented—

Treatment which is given to the pregnant woman with syphilis seeks solely to prevent infection of the unborn child or to "cure" the fetal infection if it has already occurred. The pressing problem is the welfare of the fetus and special forms of treatment desirable for the mother may be given after pregnancy is terminated. For this reason the drugs selected should be those most effective in combating acute syphilis, *i. e.*, the trivalent arsenical compounds and bismuth.

1. *Arsenicals*—Among the numerous arsenical compounds which are proposed for syphilotherapy, there are 3 from which the practitioner should make his choice for the treatment of pregnant women with syphilis. There is no well documented information to indicate a

radical difference in the syphilotherapeutic properties of these 3 drugs in the prevention of congenital syphilis and it is strongly recommended that the physician adopt and utilize the one which to him seems the most convenient and desirable. These compounds are:

(a) *Arsphenamine* (606)—This is to be given in doses of 5 to 6 $\frac{1}{2}$  grains (0.3 to 0.4 Gm.) at weekly intervals.

(b) *Neoarsphenamine* (914)—This drug should also be administered weekly in doses of 7 to 10 grains (0.45 to 0.6 Gm.).

(c) *Mapharsen*—This drug should be administered in doses of  $\frac{2}{3}$  to 1 grain (0.040 to 0.060 Gm.), and since it is more rapidly excreted than arsphenamine or neoarsphenamine, it is permissible and perhaps desirable to administer it at intervals of 4 or 5 days.

2. *Bismuth Preparation*—There is no necessity in the treatment of syphilis in the pregnant woman for employing the more unusual compounds of bismuth. Bismuth subsalicylate suspension in oil is quite satisfactory for all purposes and should be employed in a dose which is equivalent to 3 grains (0.2 Gm.) of bismuth subsalicylate, or approximately 2 grains (0.13 Gm.) of metallic bismuth. It must be pointed out that since reliable manufacturers are placing upon the market bismuth subsalicylate suspensions in oil which vary widely in the content of the drug in the vehicle, the physician must be careful to read the label. The proper dose is determined not by the number of cubic centimeters of the suspension, but by the actual amount of bismuth subsalicylate which it contains.

Appropriate treatment schemes for syphilis in mothers discovered at various stages in pregnancy are shown in Table I. In this table may be seen 3 points which must be emphasized:

(1) Regardless of the time in pregnancy at which the infection with syphilis of the mother is discovered, her treatment from that point forward should contain a maximum of treatment with an arsenical.

(2) Regardless of the duration of pregnancy at the time at which the infection with syphilis in the mother is discovered, treatment should be so planned that she will receive an arsenical in full dose for at least 6 weeks before delivery.

(3) In case the infection with syphilis in the mother is discovered late in pregnancy, simultaneous treatment with an arsenical and bismuth should be carried out.

*General Rules*—1. Make minor adjustments in time relationships by adjusting the overlap.

2. Always plan to give an arsenical for at least 6 weeks before delivery.

3. Try to administer at least 20 doses of an arsenical before delivery. If necessary, administer mapharsen every 5 days, or if very late in pregnancy, twice a week.

It is well known that there is no clinically applicable criteria for the "cure" of syphilitic infection. It follows, therefore, that every person who has ever had syphilis must be suspected of still harboring some hidden focus of *Spirochaeta pallida*, even though clinically and serologically he is well and has been well for many years. With regard to the pregnant woman, this concept becomes of extreme importance. She may have had syphilis a long time in the past and have been well treated for it; there remains, however, a small but very real chance that she may be capable of transmitting the infection to her unborn child *in utero*. It becomes obligatory, therefore, to insist that every woman who has or

TABLE I  
SCHEMES FOR TREATMENT OF SYPHILIS DISCOVERED IN VARIOUS STAGES OF PREGNANCY

Week of Gestation	Treatment of Syphilis Discovered in the First Trimester of Pregnancy	Treatment of Syphilis Discovered in the Second Trimester of Pregnancy	Week of Gestation	Treatment of Syphilis Discovered in the First Trimester of Pregnancy	Treatment of Syphilis Discovered in the Second Trimester of Pregnancy
1	As <sup>1</sup>		21	As	As
2	As		22	As	As
3	As		23	As	As Bi
4	As		24	As	Bi
5	As		25	As Bi	Bi
6	As		26	Bi	Bi
7	As		27	Bi	Bi
8	As		28	Bi	Bi
9	As		29	Bi	Bi
10	As Bi <sup>2</sup>		30	Bi	Bi
11	Bi		31	Bi	As
12	Bi		32	As	As
13	Bi		33	As	As
14	Bi	As	34	As	As
15	Bi	As	35	As	As
16	Bi	As	36	As	As
17	Bi	As	37	As	As
18	As	As	38	As	As
19	As	As	39	As	As
20	As	As	40	As	As

<sup>1</sup> A trivalent arsenical compound—Arsphenamine in 5-grain (0.3 Gm.) dose. Neoarsphenamine in 7- to 10-grain (0.45 to 0.6 Gm.) dose. Mapharsen in  $\frac{3}{8}$  to 1-grain (0.04 to 0.06 Gm.) dose.

<sup>2</sup> Bismuth subsalicylate suspension in oil in 3-grain (0.2 Gm.) dose.

has had syphilis must receive antisyphilitic treatment during every pregnancy, irrespective of the amount of treatment which she has had in the past and irrespective of her apparent clinical status, provided she shows no evidence that she is intolerant to the treatment. This is said advisedly and with the full hope that amplification of available information in the future will allow a modification of this particularly severe rule.

With the emphasis which is being placed at present upon the necessity of examining the cerebrospinal fluid in all patients with syphilis, there is sometimes the temptation to capitalize the patient's immediate co-operativeness in order to complete the record. It must not be forgotten, however, that since the treatment of the pregnant syphilitic woman is directed entirely toward the fetus and

not towards the syphilitic infection of the mother, lumbar puncture during the pregnancy is both unnecessary for collateral reasons and actually may be undesirable. Examination of the cerebrospinal fluid should be deferred to the puerperium or later, when it should be performed routinely as in all other patients.

*Summary*—1. Prenatal syphilis is a preventable disease; its prevention depends upon the routine, early, and repeated use of the serologic test for syphilis in every pregnant woman and, once the diagnosis is made in the mother, on adequate, early, and continuous treatment of the mother up to the termination of the pregnancy.

2. The pregnant syphilitic woman tolerates antisyphilitic treatment as well as the nonpregnant woman, or man; therefore, for the sake of the expected child,

treatment should be as intensive as possible.

3. The treatment of the pregnant syphilitic woman should depend primarily upon the arsenicals because of their spirocheticidal effect, and the effort should be made to administer before delivery at least 20 doses of a trivalent arsenic compound to every pregnant woman with syphilis.

4. Treatment with an arsenical should be supplemented by the intramuscular injection of an insoluble bismuth compound; this should be given between courses of the arsenical if time permits, otherwise concurrently.

5. The welfare of the mother as well as that of the child should be considered and treatment individualized to a sufficient extent to prevent untoward reactions. If the mother shows signs of being unable to tolerate the maximum treatment recommended for the majority of cases, it should be reduced until it is well borne.

#### ***Treatment of Congenital Syphilis***

—In the same pamphlet<sup>10</sup> the physician treating congenital syphilis is advised to select a few antisyphilitic remedies and know them well. Instead of attempting to cover the field of arsenic and bismuth preparations, he is wiser to choose 2 or 3 potent compounds which are low in toxicity and low in reaction-producing capabilities and administer only these.

The same arsenic preparations which are recommended for the treatment of the syphilitic mother during pregnancy are also suitable with appropriate adjustment of dosage for the treatment of congenital syphilis in infancy and childhood. In addition, sulfarsphenamine is suitable for *intramuscular use only* in infants, in whom the technical problems of weekly venepuncture are too great. The appropriate dosages of these drugs are shown in Table II.

TABLE II  
DOSE (BASED ON BODY WEIGHT) OF 4  
ARSENICALS USED IN TREATMENT  
OF CONGENITAL SYPHILIS

Drug	Dose	
	Milligrams per Kilogram Body Weight	Grams for 11 Pounds (5 kg.)
Arsphenamine	5-7.5	0.025-0.0375
Mapharsen..	0.5-1.0	0.0025-0.005
Neoarsphenamine ..	10-15	0.050-0.075
Sulfarsphenamine..	10-15	0.050-0.075

*Bismuth Preparations*—For routine use the standard preparations of bismuth subsalicylate suspension in oil are quite suitable. The proper dose is  $\frac{1}{32}$  grain (0.002 Gm.) of the compound per kilogram of body weight which amounts to  $\frac{1}{6}$  grain (0.010 Gm.) per 11 pounds of body weight. Here also it must be noted that manufacturers are placing upon the market suspensions with a widely varying concentration of bismuth. *The physician must read the label.*

*Technic of Treatment*—In general, the technic of antisyphilitic treatment in infants and small children is exactly the same as that used in adults, with the obviously necessary modifications which are dictated by the difference in the size of the patient. In infants and young children, however, if intravenous treatment is considered necessary, it may be given best into the jugular vein by the following technic: The child is laid on a table with the head dependent and turned to the left or right side. If he does not cry spontaneously during this maneuver, it is desirable to make him do so; this brings out the jugular vein very prominently and makes intravenous treatment easy. Under no circumstances should the physician attempt to give an intravenous injection into the fontanel.

TABLE III  
SUGGESTED SCHEME FOR TREATMENT OF  
CONGENITAL SYPHILIS

Week	Treatment
1	Arsenical in one-third to one-half full dose *
2-10	Arsenical in full dose.
10-19	Bismuth—note overlap.
20-29	Arsenical.
29-40	Bismuth—note overlap
41-48	Arsenical.
48-59	Bismuth—note overlap.
60-65	Arsenical.
65-72	Bismuth—note overlap.

\* It is desirable to institute treatment even more cautiously in infants ill with active early congenital syphilis.

*Reaction to Treatment*—In general, infants and small children withstand anti-syphilitic treatment well. The reactions which they suffer are identical with or similar to those seen in adults and are to be managed by the same methods. The infant who is ill with early congenital syphilis may, however, do badly under routine antisiphilitic treatment. It is wise, therefore, in instituting the treatment of such patients to practice caution, beginning with heavy metal in small doses rather than with the arsenicals and seeking at first only to prevent further progression, deferring intensive treatment until the general condition of the infant has been improved.

*Suggested Systems of Treatment for Infants and Children*—In Table III will be found a suggested scheme of treatment for infants and children with congenital syphilis. This basic system, which may be employed for children of any age by simply adjusting dosage on the basis of the patient's weight, provides for the administration of 34 doses of an arsenical and 43 of bismuth in 72 weeks.

*Management of Latent Syphilis*—In this inactive or quiescent phase of syphilis there are no symptoms which make the patient seek the aid of a physi-

cian. Latency may, however, end at any time and be replaced by active syphilis and the physician must convince a patient with quiescent syphilis that treatment during this period will in all probability forestall future trouble. Silvers,<sup>11</sup> in discussing the management of the case of latent syphilis, advises the following treatment:

Each case must be studied individually before any treatment is instituted, considering the age of the patient and the duration of the infection. It is difficult to convince the patient who has been symptom-free for many years that he should undergo a regular course of treatment.

"Early latent syphilis must be treated vigorously, for the disease is still young enough to permit hope for a clinical cure. The patient's life expectancy may still reach for many decades, during which time late syphilis or neurosyphilis may develop with its tragic consequences. Treatment, therefore, should be continuous for a period of 1½ to 2 years, during which time at least 20 or more injections of an *arsenical* should be used in addition to the *heavy metals* and *iodides*. The patient should be followed up for a number of years and watched for symptoms and signs of neurosyphilis. The problem becomes more complex in late latent syphilis.

"It must be realized that in this phase of the disease concern is mainly with the maintenance of good health and the prevention of relapses and progressiveness of the disease. To accomplish this aim, treatment must be as conservative and individualized as is deemed wise. . . .

"The Wassermann reaction of the blood can be no criterion of the amount of treatment to be given, or of the possible prognosis in latent syphilis. Moore and Padgett have shown that progression or relapse developed in 4.6 per cent of

patients with latent syphilis who were seroresistant and in 5.7 per cent of patients who were not seroresistant. Chargin and Rosenthal studied the behavior of the Wassermann reaction of the blood in 500 patients with latent syphilis who were treated mainly by the intermittent method. Ten per cent of these showed a reversal of the Wassermann reaction. In 23 per cent of the cases, the Wassermann reaction remained persistently positive. In 67 per cent, the reaction fluctuated from that of positive to weak-positive, then to negative, and from negative to positive, so that no definite conclusion could be drawn from the Wassermann reaction of the blood."

Moore and his associates found that *bismuth therapy alone* was about twice as good in the treatment of latent syphilis as any combination of an arsenical with bismuth or mercury. O'Leary does not treat latent syphilis in patients over 60 years of age or when the infection has been present for more than 30 years. *Pregnancy* in a patient with latent syphilis indicates vigorous treatment with an *arsenical and heavy metal*.

*Mapharsen in Treatment of Patients Following Arsphenamine Dermatitis*—The choice of a drug for the treatment of patients who have suffered an arsphenamine dermatitis is often difficult, particularly when it is important that the individual should have further arsenical therapy.

Summarizing reports of 17 cases from the literature of Schoch, Alexander and Long,<sup>12</sup> they found that after recovering from severe exfoliative dermatitis following arsphenamine therapy, 1 patient tolerated mapharsen and 10 did not; after recovery from mild arsphenamine dermatitis, 5 patients tolerated mapharsen and 1 did not.

The authors report their study of 40 patients who, after recovery from

arsphenamine dermatitis, were treated with small, gradually increasing doses of mapharsen. Their conclusions from this study were: (1) Mapharsen can usually be successfully administered to patients after recovery from arsphenamine dermatitis produced by neoarsphenamine, provided the dermatitis is of lesser severity than severe exudative exfoliative dermatitis necessitating hospitalization. The initial dose recommended is  $\frac{1}{65}$  grain (1 mg.) and should not exceed  $\frac{1}{12}$  grain (5 mg.). (2) Mapharsen cannot be administered successfully even in minute doses to patients who have recovered from severe exudative exfoliative dermatitis due to neoarsphenamine. In intravenous testing with mapharsen, if attempted, the initial dose should not exceed  $\frac{1}{650}$  grain (0.1 mg.). (3) Patch tests with mapharsen (3.3 per cent solution) are a more reliable guide to further therapy with mapharsen than are patch tests with neoarsphenamine.

*Value of Liver Extract in Cases Intolerant to Arsenicals*—In an investigation of the value of liver extracts as a therapeutic or prophylactic agent in cases intolerant to arsenicals and heavy metals, MacKee and Astrachan<sup>13</sup> drew the following conclusions: Liver extract is a useful therapeutic agent in some patients suffering from manifestations of intolerance due to arsenicals, heavy metals, or radiation. It is a useful supportive measure in patients with a history of previous intolerance to drugs and in those with low resistance presenting difficult therapeutic problems. The results of the investigation of the prophylactic value in patients to arsenicals or heavy metals indicate that liver extract may be of some value in preventing or ameliorating pruritus, gastrointestinal disturbance, nephritis, pains in the bones, joints and in some cases of erythema with or without scaling; it was of no value

in preventing nitritoid crises. There were more improved cases among those patients intolerant to arsenicals (58 per cent) than among patients intolerant to heavy metals (40 per cent), and the best results were obtained (improvement 71 per cent) in patients who received the largest number of liver extract injections.

Liver extract was used in some cases as a prophylactic remedy, in others, as a therapeutic agent to ameliorate after-effects of existing intolerance to arsenicals. A third group comprised cases in which no intolerance to any drug was established but which presented potential treatment problems.

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## NEUROLOGY

*Edited by* BERNARD J. ALPERS, M.D. Sc.D.

**Introduction**—During the past year important advances have been made in many fields of neurology. Much new therapy has been advocated, some of which has already demonstrated its usefulness, while other forms still remain to be tested in the crucible of time. On the whole, the trend is definitely encouraging in a field which contains so many ex-

amples of what ordinarily are regarded as hopeless cases.

In the following brief surveys no effort is made to present a complete review of the literature; only the more significant advances made during the course of the year will be mentioned, in particular those which appear to have direct clinical bearing.

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## ACUTE ENCEPHALITIS

*By* H. EDWARD YASKIN, M.D.

### Equine Encephalitis

Farber and his co-workers<sup>1</sup> published a summary of the clinical and pathologic observations made on 8 infants and children who were infected with the eastern variety of the virus of equine encephalitis. In all the cases there was a striking uniformity in the mode of onset, course and results of laboratory studies. The

onset was abrupt and pointed to an early and severe invasion of, and injury to, the central nervous system. The onset was characterized by high fever, emesis, rapid appearance of drowsiness or coma and, finally, muscular twitching or severe generalized convulsions, all becoming manifest in from 24 to 48 hours. One phenomenon was the appearance in 5 of

the patients of a nonpitting edema of the extremities, face and periorbital regions, occurring usually from 2 to 4 days after the onset of the illnesses. The clinical course in fatal cases was fulminating; 5 of the patients died. Laboratory studies showed the initial spinal fluid pressure to be elevated in 6 of the 7 patients who were examined. The initial cell counts varied from 246 white cells per cubic millimeter to 2000 white cells. The average cell count of the spinal fluid for the group was 1000 white cells per cubic millimeter. Polymorphonuclear cells predominated in the spinal fluid cell counts with percentages ranging from 60 to 100 per cent. All the spinal fluids contained increased protein, normal sugar values (qualitative tests), and no bacteria, either by direct examination or on culture. The white blood cell counts varied from 13,600 to 35,600 per cubic millimeter with a mean of 21,000. In the differential counts the polymorphonuclear cells ranged from 55 to 89 per cent. The confirmation of the diagnosis was made by isolation of the virus in 3 cases, neutralization test in 3 cases and by the pathologic examination in 4 cases. The pathologic picture in those cases which were studied was that of a severe diffuse meningoencephalitis.

#### **Toxoplasmic Encephalomyelitis**

Wolf and his co-workers<sup>2</sup> encountered a case of granulomatous encephalomyelitis due to a protozoon. The patient was

a 3-day-old infant who developed convulsive seizures, disturbances in respiration and symptoms of involvement of the spinal cord. The patient died and examination revealed a widespread encephalomyelitis characterized by multiple focal areas of inflammation and necrosis, and disseminated miliary granulomas. The protozoon parasites were found present in the leptomeningeal and parenchymal exudates, and in the granulomas. They transmitted the infection to rabbits and mice and identified the causative microorganism as a toxoplasma. It is suggested that the organism be designated *Toxoplasma hominis*. Since the lesions were confined to the central nervous system, the disease is called toxoplasmic encephalomyelitis.

#### **Acute Encephalitis**

**Treatment**—The successful treatment of a group of cases of acute encephalitis by the intravenous injection of hypotonic salt solution is reported by Retan.<sup>3</sup> He used a 0.375 per cent *sodium chloride solution*. The amount and rapidity of the intravenous injection are estimated by the weight of the patient, the behavior of the blood-pressure and the state of hydration of the patient. The author believes the efficacy of this therapy to be dependent upon the reduction of inflammatory reaction, coincident with the increased interchange of fluid between the intracellular and pericellular fluid spaces.

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## **ALCOHOLIC ENCEPHALOPATHIES**

By BERNARD J. ALPERS, M.D., Sc.D.

There have been many studies in the past few years on the treatment of alcoholic encephalopathies of all sorts.

#### **Delirium Tremens**

**Treatment**—Jellinek and Jolliffe<sup>4</sup> state that "next to acute intoxication, delirium tremens is probably the most



frequent symptom of alcoholism in general hospitals. In the past few years the tendency has developed to treat cases of delirium tremens with hydration instead of dehydration, the assumption being that such patients need fluids.

Many important articles have appeared on the treatment of delirium tremens in the past few years. The various problems are reviewed by Wortis,<sup>5</sup> who summarizes the treatment as follows: (1) The *abolition of restraints* in order to prevent the exhaustion which results from attempts to free oneself with subsequent dehydration; (2) the judicious use of *sedatives*. Morphine is definitely *contraindicated* because it embarrasses respiration and raises cerebral pressure, and because it may mask cerebral and abdominal complications. *Paraldehyde* (2 to 3 drams—8 to 12 cc.) in repeated doses has been found to be the best treatment. (3) The supplying of *carbohydrates* because of the tendency of alcohol to decrease the oxygen consumption of the brain, and to decrease the respiratory quotient. Since brain metabolism is known to depend on carbohydrates, the administration of carbohydrates as *orange juice* or *glucose* is advocated. If *insulin* is given in addition, it has been found that glucose, which accelerates the elimination of alcohol, speeds it up still more. (4) The administration of *sodium chloride* by mouth to combat dehydration and acidosis due to retention of CO<sub>2</sub> and the accumulation of lactic acid and acetone bodies. (5) The administration of vitamins, particularly *vitamins B and A*. Much attention has been directed to a possible thiamin deficiency in delirium tremens. The problem is not yet settled. Wortis states that "deficiency of vitamin B<sub>1</sub> and nicotinic acid is not specific in the causation of delirium tremens nor administration of

these vitamins in the treatment of the disease" They are, however, invaluable for certain other syndromes which frequently complicate the delirious episode or develop during the delirium. (6) A *high vitamin diet*. (7) Relative *hydration* (3000 to 4000 cc. per day).

The rôle of vitamin B<sub>1</sub> deficiency in delirium tremens is emphasized by Kiene, Streitwieser and Miller,<sup>6</sup> who regard B<sub>1</sub> deficiency as the principal factor in the production of delirium tremens. Of 10 cases treated, 5 with varying amounts of *vitamin B<sub>1</sub> and whiskey* and 5 without vitamin therapy, those with vitamin and whiskey showed an almost immediate improvement mentally and physically (24 to 36 hours), while the control cases cleared more slowly (2 to 4 days).

The importance of general medical care in the treatment of delirium tremens is emphasized by Rosenbaum, Piker and Lederer,<sup>7</sup> who reviewed 524 cases of this disorder. They found only 4 factors common to all the treatments used, *i. e.*, *hospital care, paraldehyde, lumbar puncture, and psychotherapy*. They emphasize particularly the latter. The results seem to indicate that so long as no measures are instituted that are actually injurious, adequate general medical and psychiatric care should serve to keep the mortality of uncomplicated delirium tremens down to a minimum. The mortality for the entire series was 3.5 per cent and for the past 4½ years it was 1.3 per cent. The principles underlying treatment consists of safeguarding the patient, preventing exhaustion, promoting elimination, decreasing cerebral edema, and promoting nutrition. In the authors' experience, once the disease starts, the addition of vitamin B<sub>1</sub>, nicotinic acid, liver extract, and Brewer's yeast does not seem to aid in shortening the illness.

### Nicotinic Acid Deficiency

**Encephalopathy**—Under this heading Jolliffe, Bowman, Rosenblum and Fern describe 150 cases of an encephalopathic alcoholic syndrome heretofore almost always fatal, which they believe to be due to nicotinic acid deficiency. The clinical syndrome is featured by clouding of consciousness, cogwheel rigidities, and uncontrollable grasping and sucking reflexes. It occurs not only in alcoholics, but in pellagrins as well. Prior to 1933, almost all patients with this syndrome on the authors' service died. Most of them had polyneuritis. Of 22 cases with this syndrome which were treated by the authors, 7, or 31.8 per cent, died; 4, however, died from other causes, giving a corrected mortality of 13.6 per cent. They were treated as follows: (1) On admission 6 ounces (180 cc.) an hour of 5 per cent *glucose in saline*; (2) a basal *diet* low in the vitamin B complex, if they were able to eat; (3) *nicotinic acid* as soon as the diagnosis was made in 19 cases and after 3 days in 3 others.

At first the dosage was  $7\frac{1}{2}$  grains (500 mg.) per day, increased later to 15 grains (1000 mg.) given 10 times a day in hourly doses. After recovery was definite in 3 to 5 days, a *high caloric diet* was given with  $4\frac{1}{2}$  drams (18 Gm.) of *vegex*, the nicotinic acid being continued in smaller doses for 2 to 10 days longer. The results of the treatment are incomparably better than in cases not treated with nicotinic acid. The authors regard this group of cases as a special type of encephalopathy in the alcohol group, due to nicotinic acid deficiency.

### Korsakoff Syndrome

**Treatment**—As Jellinek and Jolliffe remark, "all reports published during the past year (1939) mention the use of either vitamin B complex or vitamin B<sub>1</sub> in the therapy of the Korsakoff psychosis." There appears to be much greater success in therapy when *vitamin B* is used in the treatment of this disease. This opinion is confirmed by the experience of others.

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## EPILEPSY

By BERNARD J. ALPERS, M.D., Sc.D.

**Treatment with Dilantin**—The search for an effective means of controlling epilepsy will continue until it is hoped this dreaded disease is eventually brought under control. Since the introduction of *dilantin* in 1937 by Merritt and Putnam, this drug has been in wide use for the control of epileptic attacks. Dilantin is dispensed in  $1\frac{1}{2}$  grain (0.1 Gm.) capsules in dosages of 3 capsules a day. When it is given as a substitute for other drugs, it should be substituted gradually. During the past year there have been many reports of its usefulness, of which only the more important can be reviewed. The latest

report by Merritt and Putnam<sup>9</sup> records the following results:

They treated 267 patients refractory to other forms of treatment. One hundred and sixty-four of the patients were subject to only 1 type of attack at the time dilantin therapy was instituted: 124 had *grand mal*, 21 *petit mal*, while 19 had psychic equivalent or psychomotor attacks. The remaining 103 suffered from a combination of the 3 types. Dilantin was most effective in controlling "psychic equivalent" attacks (12 of 19 completely relieved), next most effective in preventing "*grand mal*" attacks (74 of 124 cases completely relieved), and

least effective in the "*petit mal*" attacks (6 of 21 completely relieved). Of 20 other patients with psychic equivalents associated with *grand mal* attacks, 12 were completely relieved; of 103 with *grand mal* attacks associated with *petit mal* or psychic equivalents, 63 were completely relieved, and such relief occurred in 34 of 83 patients with *petit mal* associated with *grand mal* seizures. Putnam and Merritt speak therefore for the greater effectiveness of dilantin in the treatment of epilepsy.

Butter<sup>10</sup> followed 43 cases of epilepsy for 1 year and found great improvement in 46.5 per cent; improvement in 16 per cent; no change in 13 per cent; while 2 per cent were worse. Frankel<sup>11</sup> treated 48 cases from 3 to 18 months and found entire control of the attacks in 39 per cent, alleviation in 21 per cent, and no benefit in 39 per cent.

The question has been raised whether the results of dilantin are indeed as remarkable as they seem or whether phenobarbital has not been used in maximum doses. Granting that this may be so, there is no doubt that dilantin is superior to phenobarbital in that it has none of the unpleasant drowsiness associated with the latter, and leads to none of the mental dullness which is so often seen with prolonged phenobarbital dosage. Some doubt concerning the overwhelming virtues of dilantin is cast by the report of Pratt,<sup>12</sup> who studied 52 cases which had shown no response to phenobarbital or other barbiturates. These cases were treated with dilantin for 2 to 10 months with the following results:

	No. of Cases	Per Cent
Controlled for 2 months or longer	6	11.5
Markedly reduced. . . . .	11	21.2
Little or no reduction. . . . .	35	67.3

A somewhat similar doubt is mentioned by Cohen, Showstack, and Myerson,<sup>13</sup> who found that when dilantin was substituted for phenobarbital in a group of 18 epileptics, there was a definite increase in the number of seizures. They believe, therefore, that dilantin alone has not exerted as favorable an effect in reducing seizure incidence as adequate phenobarbital dosage. On the other hand, their studies show that in another group of 23 epileptics, the addition of dilantin to the phenobarbital medication resulted in a reduction of seizures amounting to 50 per cent. They assert, therefore, the combination of *dilantin and phenobarbital* "is far more efficient than either drug used alone, the reduction in seizure incidence being at least 50 per cent over the most favorable results obtained without the synergistic use of these drugs."

Blair<sup>14</sup> has made a careful analysis of the effects of *dilantin* and found in 36 cases of chronic epilepsy, of whom 20 were treated for over a year, that there was an absolute reduction of fits in 1 case, a reduction of 75 per cent in 6 cases, between 50 and 75 per cent in 5 cases, between 25 and 50 per cent in 2 cases, and a slight increase in 1 case. Toxic symptoms were found to be numerous and always occurred soon after the introduction of dilantin or after an increase in dosage. All of Blair's cases were psychotic. Blair studied the comparative efficacy of the various therapeutic remedies for epilepsy. He makes the important point that "the ideal treatment for any individual patient will vary according to his idiosyncrasy for the various anticonvulsant drugs." He regards dilantin as a powerful anticonvulsant, with little, if any, sedative or hypnotic effects. He regards *bromides* as of definite value in some cases. According to Blair, *pheno-*

*barbital* is probably the most useful of the anticonvulsants. "To get its best effects, however, it is necessary in many cases to use massive doses even up to 10 grams (106 Gm.) per diem." Some cases do better on a combination of drugs, as for example *phenobarbital and dilantin*, or *phenobarbital and bromides*. According to Blair, "when confronted with a case of epilepsy which has not been treated previously with anticonvulsants the order in which these drugs may be most advantageously tried out would seem to be, broadly speaking, (1) luminal (phenobarbital), (2) epanutin (dilantin), (3) a combination of luminal and epanutin, (4) bromides alone or in combination with one of the others, (5) prominal."

The results of Fetterman<sup>15</sup> with *dilantin* are more favorable than those

of Blair. In 28 cases of chronic epilepsy treated for 2 years with dilantin Fetterman reports excellent results in 10 cases which had been refractory to other forms of treatment, moderately good effects in 2 cases, fair results in 3, no effect in 1, slight benefit in 2, and a harmful reaction in 2 cases. Four cases were tabulated as doubtful because of side reactions, though all experienced a reduction in seizures. The treatment was discontinued in 5 cases. Fetterman regards dilantin as an anticonvulsant superior to phenobarbital, and to phenobarbital and bromides combined.

Lennox<sup>16</sup> in his report points out that dilantin has 2 advantages over bromides or phenobarbital: it is not a sedative and its use in maximum doses is not accompanied by dulling of the mental faculties.

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## MENINGITIS

By BERNARD J. ALPERS, M.D., Sc.D.

### Sulphonamide Compounds in Treatment

#### 1. Meningococcic Meningitis —

Since the introduction of sulfanilamide and its related compounds, the treatment of this form of meningitis as well as of many other forms has come to be much more encouraging than ever before. The subject has been authoritatively and exhaustively reviewed by Kolmer.<sup>17</sup> He finds that sulfanilamide is highly effective in meningococcic meningitis. Kolmer states that "on the basis of mortality rates, the results have been equal to and in some instances decidedly better than those observed with serum treatment, and sulfapyridine may be even more effective than sulfanilamide." The optimum method of administration and the indications for serum treatment are

not yet agreed on. In mild or average cases Kolmer believes that sulfanilamide in maximum dosage by oral administration alone appears to be sufficient when a concentration of at least 5 mg. of free sulfanilamide per 100 cc. of spinal fluid can be secured and maintained for at least 3 days. In comatose and vomiting patients parenteral administration is necessary. Banks<sup>18</sup> treated 65 cases of *acute meningococcic meningitis* with *serum and sulfanilamide* with only 8 deaths (12.3 per cent). He treated 31 cases with *sulfanilamide* alone, 36 with *sulfapyridine*, and 5 with a combination of the 2 drugs, with only 1 death. He found the oral route could be used in most cases.

Jordan, Blakelock and Johnston<sup>19</sup> compared the effects of sulfapyridine

with those of serum in meningococcic meningitis. Fifty patients were studied in each group. The *serum* was given in 20 cc. doses intrathecally every 12 hours until improvement occurred and then every 24 hours. *Sulfapyridine* was given in dosages of 4 tablets ( $7\frac{1}{2}$  grains—0.5 Gm. each) on admission, repeated after 4 hours, followed by 2 tablets every 4 hours for 24 hours, followed by 1 tablet thrice daily. The fatality rate was 38 per cent for the serum cases and 32 per cent for the sulfapyridine group. The authors then studied 60 cases treated with both serum and sulfapyridine, 1 group of 30 cases receiving serum and sulfapyridine and another group of 30 cases antitoxin and sulfapyridine. The mortality rate was 26.2 per cent and 20 per cent, respectively.

Todesco<sup>20</sup> treated 31 patients of meningococcic meningitis with *M & B 693* (*sulfapyridine*) and *meningococcus antitoxin*. There were 7 deaths, chiefly among patients admitted to the hospital in a late stage of the disease. He gave sulfapyridine (30 grains—2 Gm.) on admission and repeated in 4 hours, followed by 15 grains (1 Gm.) every 4 hours for 36 hours, then  $7\frac{1}{2}$  grains (0.5 Gm.) 3 times a day for 24 hours. Children received one-half this dosage. The meningococcus antitoxin was given intrathecally in dosages of 20 to 40 cm.

Excellent results with sulfapyridine are reported by Jäckli<sup>21</sup> in the treatment of meningococcic meningitis in children, all of whom recovered. The drug was given in dosages of 15 grains (1 Gm.) for each 10 kg. of body weight.

Ten cases of meningococcic meningitis were treated by Rusesco, Voiculesco and Diaconu<sup>22</sup> with *sulfanilamide*, 9 of whom recovered. The authors suggest the treatment of meningococcic meningitis by sulfanilamide alone and suggest

combining it with serum therapy only in cases which do not tolerate sulfanilamide.

2. **Pneumococcic Meningitis**—Kolmer states that the use of sulfanilamide and sulfapyridine has materially reduced the mortality in pneumococcic meningitis. He believes that *sulfapyridine* is the compound of choice. Rhoads<sup>23</sup> and his colleagues report 22 cases of pneumococcic meningitis, 7 of whom recovered. The diagnosis of this form of meningitis having been established, the sodium salt of sulfapyridine in doses of 60 to 90 grains (4 to 6 Gm.) in 5 per cent solution is given intravenously. This is repeated every 12 hours until a blood level of 10 to 20 mg. per 100 cc. is attained. Usually large doses up to 30 grains (2 Gm.) every 4 hours, day and night, by mouth, are required to keep the level at this figure for the first few days. Later, doses of 15 to 23 grains (1 to 1.5 Gm.) every 4 hours may suffice. For children the dosage is calculated on the basis of 1 to  $1\frac{1}{2}$  grains (0.06 to 0.1 Gm.) per pound of body weight for 24 hours, the dose being divided equally into 6 parts and administered every 4 hours, after an initial dose equaling one-half the calculated day's dosage. Sulfapyridine is continued until the temperature has been normal for several days and until the spinal fluid and blood cultures are sterile. *Specific antipneumococcic rabbit serum* is given intravenously as soon as the organism is typed.

Hodes, Gimbel and Burnett<sup>24</sup> report 17 cases of pneumococcic meningitis treated with *sulfapyridine* by mouth and intravenously. They report 8 recoveries. Sherman<sup>25</sup> reports a case of pneumococcic meningitis which recovered with *pneumococcic serum and sulfapyridine*.

The number of cases reported is still small but there appears to be good rea-

son to hope for further successes with sulfapyridine treatment with or without the use of specific serum.

**3 Influenzal Meningitis**—Silverthorne,<sup>26</sup> reports a case of influenzal meningitis successfully treated with *sulfapyridine*. Arnett, Shoup and Henry<sup>27</sup> found 25 cases of influenzal meningitis up to 1940 treated with sulfapyridine, with 14 recoveries. This mortality of

44 per cent is in marked contrast to a previous mortality of 82 per cent and 98 per cent in cases treated with and without specific serum. Sulfanilamide has been used in treatment, but the results are not as impressive as with sulfapyridine. Arnett, Shoup and Henry record another case of influenzal meningitis treated successfully with sulfapyridine.

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## MIGRAINE

By HERBERT S. GASKILL, A.B., M.D.

**Diagnosis**—The classical picture of migraine, according to Lyon,<sup>28</sup> is seen in an individual who has a family history of migraine. The onset of the attacks is early in life with periodic episodes of headache, generally unilateral, and most frequently accompanied by nausea and vomiting. Generally there are prodromes such as visual phenomena. Between attacks the patient is entirely free from symptoms. Migraine is more common in women. Many patients do not present the entire picture or have certain variants, but the more their syndrome deviates from the usual picture, the less likely is their headache to be a true migraine attack.

**Etiology**—Many factors have been implicated as the cause of migraine but few are capable of being proven. Lyon emphasizes nervous and alimentary conditions as precipitating factors in inducing an attack of migraine. Alvarez<sup>29</sup> confirms this opinion concerning the constitutional factor. He believes that migraine is more prone to occur in individuals who are overly reactive to emotion and overly sensitive to all stimuli, who are too conscientious, overwork and take life too seriously.

Lennox<sup>16</sup> believes that there is some relationship between migraine and epilepsy. In a group of patients who had migraine he found an incidence of seizures 12 times that of a control group; moreover, among their relatives the incidence of epilepsy was 3.6 times that of the controls. He found, in addition, that migraine occurred twice as frequently among epileptics as it did in a control series; and that the relatives of these epileptics had migraine twice as frequently as in the relatives of the control group. Gardner, Mountain and Hines<sup>30</sup> suggest that there may be a connection between hypertension and migraine. In 100 cases of hypertension, 79 had a history of migraine, whereas only 15 cases occurred in a control series. As additional evidence they found that during the year 1938 the diagnosis of migraine was made 5 times more frequently in patients with than in those without hypertension.

Because of the associated biliousness, migraine has frequently been attributed to disease of the liver. Morloch and Alvarez<sup>31</sup> studied 215 cases with disease of the liver, *i. e.*, cirrhosis of the liver and biliary tract disease, and found migraine in only 7 per cent of the cases.



no use as an interval treatment. Ergotamine orally has no effect, since it is poorly absorbed and generally causes marked vomiting.

The effect of *ergonovine hydracrylate* on migraine attacks has been studied by Lennox and Sutherland and Wolff. It is effective in only about 40 to 50 per cent of cases of migraine. The drug has less unpleasant side effects so that it is to be preferred in those cases in which it is effective. It has the additional value that since it does not cause nausea and vomiting, it may be given by mouth as well as intramuscularly. The oral preparations go under the trade names of *ergometrine*, *ergobasine tartrate*, *ergotrate*, *ergoklonin*—the dosage is  $\frac{1}{12}$  to  $\frac{1}{6}$  grain (5 to 10 mg.) during an attack. The dosage for intramuscular use is the same as for ergotamine tartrate.

Sutherland and Wolff made comparative studies of the various vasoconstrictors and found that those drugs which reduce the amplitude of the pulsations in the temporal artery from 40 to 50 per cent would relieve migraine. *Caffeine with sodium benzoate* is effective if taken orally but only increases the headache if given intravenously, since it then acts as a vasodilator. *Benzedrine sulfate*  $\frac{1}{6}$  grain (10 mg.) given intramuscularly, was effective as was 20 pressor units of *pitressin*. *Ephedrine sulfate*  $\frac{1}{5}$  grain (0.013 Gm.) given intravenously, very slowly, had a temporary effect. The effectiveness of none of these drugs, however, was as certain or of as great duration as ergotamine tartrate. Drugs such as *codeine*, *acetylsalicylic acid* and *acetophenetidin* can relieve or abolish migraine headache in adequate dosage. Their action depends on raising the threshold to pain and not in correcting the pain-producing mechanism.

Palmer<sup>36</sup> has had considerable success in the treatment of migraine with *thiamin chloride*. His method of treatment consists of giving  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains (30 to 90 mg.) of thiamin chloride each day for a period of 2 weeks, increasing or decreasing the dose, depending on the severity of the condition. At the end of 2 weeks the dosage is decreased to  $\frac{1}{2}$  grain (30 mg.) intramuscularly 3 times a week for a period of 2 weeks, which is followed by  $\frac{1}{2}$  grain (30 mg.) of thiamin chloride intramuscularly once or twice a week for a period of 2 months. If during the course of treatment an attack of migraine occurs, 1 to 2 grains (60 to 120 mg.) of thiamin chloride is given intramuscularly or intravenously to terminate the headache. During the entire course of treatment large amounts of *vitamins A, B<sub>1</sub>, C, D* and *G* are given orally. The treatment should not be stopped in the absence of a favorable response in less than 3 months. If, however, the treatment is not effective at the end of 4 weeks, *liver extract* in doses of 15 U.S.P. XI units should be given intramuscularly once or twice a week. The author has treated 11 patients with migraine in this manner with success in 65 per cent of the cases.

Lennox and Alvarez have found that the inhalation of 100 per cent *oxygen* will cure migraine in a limited group of patients.

A certain number of women cease to have migraine after the menopause. Alvarez<sup>37</sup> studied the resultant effect on the migraine of 42 women who had menopause induced by operative procedure or by roentgen ray. Of these 42 cases, only 6 were relieved of their headache; 5 had less severe headache; in 16 they were better only for a short time or unchanged, and in 15 they were made worse. Three additional cases had



their first migraine attacks following an induced menopause. From this series Alvarez concluded that it was unwise to advise an artificial menopause to relieve migraine. In another article the same author comments on the fact that surgical procedures on the abdominal viscera rarely cure migraine. Moreover,

although many patients believe that certain foods are the cause of migraine, allergic studies rarely confirm this.

Nearly all the authors recommend that these patients lead *less active lives*, that they obtain adequate amounts of *exercise* and *sleep*, *avoid worry* and *do not overwork*.

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## MULTIPLE SCLEROSIS

By H EDWARD YASKIN, M.D.

**Pathogenesis**—Friedman<sup>38</sup> has reviewed the literature on the relationship of *trauma* to the occurrence of multiple sclerosis. He found that statistical studies of various authors showed the incidence of trauma to be 8 to 10 per cent of the cases of multiple sclerosis. His own experience in a series of 61 cases seemed to confirm this percentage incidence. On the basis of a survey of the literature and of his own cases, he concludes that there is no absolute warrant for the belief that multiple sclerosis can arise as a result of trauma *per se*. Trauma can play an important rôle, however, as a precipitating factor in latent disease and as an aggravating factor in disease already present.

**Treatment**—Moore,<sup>39</sup> in a preliminary report, believes that a combined administration of *nicotinic acid* and *thiamin chloride* has yielded promising results in a series of 5 cases. The rationale of this therapy was the thought that a hyperemia of the central nervous system could be effected with nicotinic acid similar to that observed in the skin. The causation of vasodilatation by the drug may effect amelioration of the lesions, due to increased oxidation and improved nutrition. The medication was given parenterally. Moore utilized 2 methods of administration. He gave 1¼

to 2¼ grains (80 to 140 mg.) of nicotinic acid intramuscularly 2 or 3 times a week, depending on the reaction of the patient. At the same time he administered ½ grain (33.2 mg.) of thiamin chloride intravenously at the height of cutaneous hyperemia, caused by the nicotinic acid. He also utilized a method of administration wherein he injected 2½ drams (10 cc.) of a solution of sterile water containing 2 grains (120 mg.) of nicotinic acid and ½ grain (33.2 mg.) of thiamin chloride. This dose was injected into the buttock. With this treatment complete remissions were not obtained in his cases, but he felt there was continued symptomatic improvement with the therapy.

Bennett and Lewis<sup>40</sup> report the results of *artificial fever therapy* in 51 cases of multiple sclerosis, using the Kettering hypertherm. Most of the patients received a course of 6 treatments, each of 3 or 4 hours at 104° F. (40° C.), but many returned for further courses of treatment. Of 10 patients classified as early cases, 8 experienced and maintained worthwhile improvement. Of 25 patients classified as intermediate cases, 13 showed slight to marked improvement. The authors feel, however, that the results in this intermediate group are

not very different from the probable results without treatment. In 16 advanced cases only 2 showed any definite halting of the progress of their disease, and a few seemed to be made at least temporarily worse by the treatments. These authors conclude that fever therapy should be tried in early cases of short duration and in ambulatory cases with-

out assistance. In the group of multiple sclerosis cases where assistance is required for the patient to be ambulatory but not completely disabled, the benefits derived from fever therapy are doubtful. In the bedridden group, in which the disabling symptoms are of long duration, fever therapy does no good and may do harm.

## MYOPATHIES AND NUCLEAR AMYOTROPHIES

By BERNARD J. ALPERS, M.D., Sc.D

### Myopathies

**Vitamin Therapy**—The group of the myopathies or primary muscular disorders, which includes such examples as *progressive muscular dystrophy*, *pseudohypertrophic muscular dystrophy* and similar disorders, has always offered serious obstacles to treatment and has yielded barren results. Since the discovery that a nutritional muscular dystrophy could be produced in rats, guinea-pigs, rabbits and other animals maintained on a diet deficient in vitamin E, efforts have been directed to the treatment of the human myopathies with vitamin E alone or in combination with other vitamins, notably vitamin B. The myopathies were treated with (1) the *crude wheat germ oil* by mouth (1 dram—4 cc.—twice daily); 2 *alpha-tocopherol*, the synthetic active principle of vitamin E, in dosages of  $\frac{1}{3}$  grain (25 mg.) per day by mouth or intramuscular injection, or (3) by a combination of these 2 remedies. In some instances *thiamin chloride* or *vitamin B complex* was given in addition. The reported results have been conflicting, and have varied from reportedly good to poor responses to the treatment.

Bicknell,<sup>41</sup> for example, treated 18 cases of progressive muscular dystrophy with vitamin E. He gave  $\frac{1}{2}$  ounce (15

Gm.) of fresh dried *whole wheat germ* twice daily. He found that every case of myopathy improved which was treated for more than 6 weeks.

Stone<sup>42</sup> has reported startlingly good results in young patients with muscular dystrophy. He advocates the use of  $\frac{1}{2}$  dram (2 cc.) of *wheat germ oil* daily together with *vitamin B complex*. For cases of longer standing he uses 1 to  $1\frac{1}{2}$  drams (4 to 6 cc.) of wheat germ oil daily. He noted definite improvement in 5 cases of muscular dystrophy, the improvement being manifested by a gain in muscular strength, the disappearance of fatigue and muscle pain on exertion, change in muscle texture, and the displacement of dystrophic musculature by normally contracting muscle tissue.

Opposed to this is the experience of Sheldon, Butt and Woltman,<sup>43</sup> who treated 8 cases of progressive muscular dystrophy with both wheat germ oil and alpha-tocopherol without success. Similarly, Alpers, Gaskill and Cantarow<sup>44</sup> report indifferent results with vitamin E alone in the treatment of muscular dystrophies of long standing. They report 6 cases which were treated with *wheat germ oil* (2 drams—8 cc.—daily) or *alpha-tocopherol* ( $\frac{1}{3}$  grain—25 mg.—daily). In 3 of their cases there was slight but definite improvement mani-

fested by ability to climb stairs and ability to arise from a crouching position. All the cases which improved manifested a sense of well-being while under treatment with vitamin E which was not present when they were taken off this treatment. None of the cases showed a change in creatine metabolism as studied by the creatine and creatinine output in the urine.

### Nuclear Amyotrophies

**Vitamin Therapy** — In this group of diseases are included progressive muscular atrophy, amyotrophic lateral sclerosis, chronic progressive bulbar paralysis, and chronic progressive ophthalmoplegia, all of them inevitably fatal diseases. Attention has been called within the past year to the possibility of treatment of these cases, particularly amyotrophic lateral sclerosis, with vitamin E. Chief among the proponents of this treatment is Wechsler,<sup>45</sup> who has reported excellent results in some cases of *amyotrophic lateral sclerosis*, using both *vitamins E and B*. In a preliminary report he cites 2 cases of amyotrophic lateral sclerosis which responded promptly to vitamin E, particularly the synthetic tocopherols. Full recovery occurred in an early case; in another case great improvement was noted. Wechsler reports no results in a trial of vitamin E in 3 other cases. In a fourth case there seemed to be some recovery of muscle power. Withdrawal of the tocopherols resulted in return of weakness,

with return of power when treatment was resumed.

Wechsler has reported even better results in a larger group of cases of amyotrophic lateral sclerosis. In a personal communication Wechsler states that his present regimen includes at least 4 grains (250 mg.) of *synthetic vitamin E* by mouth, 3 grains (200 mg.) of *alpha-tocopherol* intramuscularly daily, 1 ounce (30 Gm.) of *wheat germ powder*, *bile salts*, and in some cases *vitamin B<sub>6</sub>*. In the *diet* he gives large amounts of foods rich in vitamin E such as lettuce, kale, whole wheat bread, coarse cereals, butter, nuts, fat beef, bananas, fresh corn, fresh green peas, and yolks of eggs.

Bicknell has also noted a slight improvement in 2 out of 4 cases of amyotrophic lateral sclerosis treated with *vitamin E*. On the other hand, Sheldon, Butt and Woltman report no improvement whatever in 6 cases of amyotrophic lateral sclerosis treated with both wheat germ oil and alpha-tocopherol.

Despite the conflicting results which have been reported, *vitamin E* therapy in amyotrophic lateral sclerosis is decidedly deserving of trial. It should be given in large doses as in the myopathies and should be combined with large doses of *thiamin chloride* ( $\frac{1}{2}$  grain—30 mg.—intramuscularly daily), *B complex* (2 capsules 3 times a day), *bile salts*, and *nicotinic acid* ( $1\frac{1}{2}$  grains—100 mg.—daily).

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## NEURITIS

By BERNARD J. ALPERS, M.D., Sc.D.

**Etiology — Sulfanilamide** — A few cases of neuritis have now been reported following the administration of sulfanilamide and there seems to be no

doubt that neuritis develops after this treatment. Wauh reports a case of peripheral neuritis with drop-foot during the treatment of gonorrhea with sulfa-

nilamide. He was able to find only 2 other cases of neuritis and 1 case of optic neuritis in the literature following the use of this drug. Wauh's case was the only instance of neuritis among 650 hospitalized patients who received intensive sulfanilamide treatment for gonorrhea or other urologic conditions. Radermecker<sup>46</sup> reports a case of multiple neuritis following the use of sulfanilamide, as does also de Monchy.<sup>47</sup>

**Cirrhosis of the Liver and Neuritis**—A relationship between cirrhosis of the liver and multiple neuritis has been suggested by Wayburn and Guerard.<sup>48</sup> They studied 272 cases of liver cirrhosis, from which were excluded cases of fatty alcoholic livers. A history of alcoholism was found in 70 per cent of their cases and multiple neuritis in 17 per cent. They regard the high incidence of liver cirrhosis as important, and found not only a history of alcoholism, but a general dietary deficiency and deficiency of thiamin intake.

**Treatment—Thiamin Chloride**—The field of neuritis is actively occupied at the moment in determining the value of thiamin chloride. There can be no doubt that vitamin B<sub>1</sub> (thiamin) deficiency is responsible for neuritis, usually a multiple neuritis. This is true, especially of the neuritis found in alcoholism, pellagra, the cachexia of carcinoma, short-circuiting operations of the bowel, pylorospasm, and beriberi, to mention only random examples. The danger lies in assuming that such a deficiency occurs in all forms of neuritis. Vorhaus<sup>49</sup> has analyzed the value of thiamin chloride in the treatment of 562 cases of neuritis of varied etiology falling into the following groups:

Toxic—heavy metals, 5; toxic—endogenous, 26; gestational, 12; metabolic, 118; nutritional, 125; infectious, 161; unknown etiology, 115.

Both natural and synthetic thiamin was used, 75 per cent of the patients receiving the vitamin orally and 25 per cent parenterally. The average daily dose varied from  $\frac{1}{20}$  to  $\frac{1}{6}$  grain (3 to 10 mg.). The response to thiamin therapy depended in part on the duration of the symptoms. Cases with symptoms of several weeks' to a few months' duration showed a quicker response than those with symptoms of years' duration. About 75 per cent of Vorhaus' cases showed improvement within 4 weeks, but 62.5 per cent developed recurrences, suggesting that the benefit derived from thiamin therapy is not permanent. Fifty per cent of patients developed recurrences within a year and 90 per cent within 3 years. Vorhaus concludes, therefore, that some patients require thiamin continuously in order to remain symptom-free. The cases with unknown etiology appeared to develop a greater incidence of recurrences.

The use of thiamin chloride in cases of *trigeminal neuralgia* has been advocated by Borsook, Kremers, and Wiggins,<sup>50</sup> who treated 58 patients with large doses of *thiamin chloride* and in some cases with concentrated *liver extracts*. The dosage used consisted of  $\frac{1}{6}$  grain (10 mg.) daily of thiamin chloride intravenously or intramuscularly. In cases which fail to respond to thiamin alone, concentrated liver extract is given 3 times a week (0.5 cc. intramuscularly). In addition, the patients were placed on a *high vitamin-low carbohydrate diet*. The 58 patients reported were under observation from 6 to 14 months. Thirty-seven are reported markedly improved, 15 improved, 3 slightly improved, and 3 not improved. Of the 52 cases which were markedly improved and improved, 38 had a remission in the course of and after active

therapy which was longer than any spontaneous remission during the 2 years prior to the beginning of treatment.

Neuritis of the *auditory nerve* has also been treated by thiamin therapy. Brandenburg<sup>51</sup> reports a case of severe bilateral tinnitus and impairment of hearing in which relief was obtained by the daily intravenous injection of thiamin chloride  $\frac{1}{6}$  to  $\frac{1}{4}$  grain (10 to 15 mg.) for 9 days. He suggests the intravenous use of thiamin chloride in 1 or more daily doses  $\frac{1}{6}$  grain (10 mg.) for all neuritis cases of the cranial nerves.

Neuritis of *ischemic origin* has been treated successfully with thiamin chloride by Naide,<sup>52</sup> who defines ischemic neuritis as a type of rest pain present in patients with extensive arterial occlusion. Thiamin was given in these cases on the

assumption that by its use in large doses the blood concentration could be raised to such a level that even the reduced blood supply in ischemic areas could maintain an adequate thiamin content. Naide gave thiamin in doses of  $1\frac{1}{2}$  grains (100 mg.) intravenously daily, every other day or twice a week. He treated 8 cases, all of whom had had severe pain from 1 month to 8 years. Of these cases, 7 were relieved of pain in from 1 day to 2 weeks; 2 cases had partial relief, and 1 case of thromboangiitis obliterans obtained no relief. All the cases had obtained no relief from other forms of treatment. Cessation of the thiamin treatment was followed by a return of pain; hence, maintenance doses of  $\frac{1}{8}$  to  $1\frac{1}{2}$  grains (20 to 100 mg.) twice a week were required in cases in which the vascular condition remained unchanged.

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## NEUROSYPHILIS

By BERNARD J. ALPERS, M.D., Sc D.

There has been no strikingly new advances in neurosyphilis in the past year, but several substantial studies are available. Moore and Woods<sup>53</sup> review the subject of *sypilitic optic atrophy*. They find that **subdural treatment with mercury** or other compounds and **malarial treatment** offer the best possibilities of success, though the results are relatively disappointing.

Berman<sup>54</sup> finds that *acute sypilitic transverse myelitis* seems to be on the wane, since only 5 cases have been reported in this country in the past 15 years. This is encouraging, since the condition is not hopeful from the standpoint of treatment. The onset is acute, is associated with flaccid paralysis of the legs, retention of urine, and a sen-

sory level. The spinal fluid changes may be strongly positive or normal.

Nineteen cases of *tabes dorsalis* were treated by Angyal and Gyafas<sup>55</sup> with **Hilgerman's** living, avirulent culture of the spirochetes. The **vaccine** was given subcutaneously in the thigh at intervals of 14 days and 1 to 12 injections were given. It was found to have a beneficial effect on the lightning pains and gastric crises of *tabes*.

Black<sup>56</sup> reports good results with **cobra venom** in the treatment of the lightning pains of *tabes*.

Kroll<sup>57</sup> recommends the use of **quartan malaria** in the treatment of *neurosyphilis*. Of 23 paretics treated, 10 showed incomplete remissions, and 5, complete return of function. Of 13

tabetics, all showed varying grades of relief and in 5 of 6 cases of optic atrophy, existing eyesight was maintained. Five cases of meningovascular syphilis all improved. The spinal fluid Wassermann reaction was affected relatively little, though other features of the spinal fluid showed changes. Kopp and Solomon<sup>58</sup> found on analysis of 302 cases of neurosyphilis treated with malaria that the best

results were obtained in patients with more than 150 hours of fever above 100° F. (37.8° C.). Patients who had more than 10 chills were improved more often than those with less. Mays, Oden and Cox<sup>59</sup> prefer quartan to tertian malaria in the treatment of general paresis because of its higher improvement rate, its lower death rate, and the more prolonged temperature elevation.

## POLIOMYELITIS

*By* HERBERT S. GASKILL, A.B., M.D.

**Diagnosis** — The diagnosis of sporadic cases of poliomyelitis has always been attended with considerable difficulty. Trask, Paul and Vignec<sup>60</sup> have demonstrated that the poliomyelitis virus can be isolated in the stools of patients ill with the disease by intracerebral or intraperitoneal injection into experimental animals. This type of inoculation requires elimination of the other intestinal flora which may kill or decrease the virulence of the poliomyelitis virus. Howe and Bodian<sup>61</sup> have eliminated this by successfully using intranasal inoculation of their monkeys. In a series of 14 cases they obtained positive results in all 7 cases when the stools were obtained in the first 5 days of the paralytic stage and in the 3 of 7 cases when the stools were obtained after the fifth paralytic day. Paul and Trask<sup>62</sup> were able to obtain positive results from cases which never developed any evidence of central nervous system involvement.

Thus, it would now appear to be possible to make the diagnosis early in an epidemic and establish infectious precautions early before the disease has an opportunity to spread widely. This also affords a method for diagnosing abortive cases and the well "carriers" who are

a potential source of danger in the spread of the disease.

**Epidemiology**—Although many factors have been indicted as the means of transmission of poliomyelitis, the only one which has been definitely proven is direct contact between individuals. Paul and Trask have been able not only to demonstrate the poliomyelitis virus in the stools of patients ill with the disease, but also in the sewage draining from hospitals having patients ill with poliomyelitis. Moreover, in the case of a small epidemic occurring in Connecticut, in 1939, there was some relationship to a common watercourse, since a great many of the cases were located along the course of a river.

The studies of Ellsworth<sup>63</sup> along this line are of considerable interest. He studied the sewage disposal of Fall River which emptied directly into the river. At some distance from these outlets there were 2 swimming beaches. Although normally the sewage did not reach these sites, at times the currents and wind carried it there. Thus, although the beaches were for the most part safe, they could upon occasion become polluted. He found, in addition, that in the poliomyelitic epidemic which

occurred in Massachusetts in the summer of 1935, the highest incidence of infection was in those communities bordering on waters used for bathing and affected by sewage pollution. Since most epidemics of poliomyelitis occur in the summer, the author raises the question as to whether water pollution may not be a considerable factor in the spread of poliomyelitis.

"An extensive study of the means of dissemination of the poliomyelitis virus has been made by Bodian and Howe.<sup>64</sup> They find that there are several routes of spread of the infection and they conclude that the virus of poliomyelitis travels through the central nervous system along certain preferential pathways determined by (a) differential susceptibility of certain centers; (b) accessibility of the virus as determined by the kind and quantity of neuronal connections between any center and other centers from which the virus can spread; and (c) portal of entry.

In the early stages of the disease the distribution and the severity of the lesions depend chiefly on the site of inoculation. In the later stages the virus usually involves all of the preferential areas, and, in addition, invades susceptible centers not included among those primarily affected, with the result that the final picture is similar, with slight differences, regardless of the portal of entry.

The evidence indicates that the virus spreads along neuronal pathways and is conducted most rapidly over short chains, where the perikarya serve to increase the connection of the infecting agent.

**Prophylaxis**—Various studies have been made of agents which would alter the metabolism and physiology of the nerve-cells sufficiently to alter the course of poliomyelitis in experimental animals.

Jungeblut<sup>65</sup> found that neither the administration of a hypnotic such as sodium luminal nor the production of systemic shock by insulin or metrazol alters the course of the disease in monkeys.

Saucier and Stewart<sup>66</sup> found that injections of potassium chlorate failed to protect monkeys against poliomyelitis, despite the good reports of Contat in the Switzerland epidemic of 1936-37.

Dalldorf<sup>67</sup> studied the immunity afforded by previous infection with another virus disease. If choriomeningitis was induced in monkeys from 1 to 10 days before they were inoculated with poliomyelitis virus, protection against the poliomyelitis was developed. He suggests that this "sparing effect" might be used as an immunological mechanism, although it does not as yet appear practical. If choriomeningitis in an abortive form is as common as Armstrong<sup>68</sup> feels it is, it may be that this mechanism is already at work.

The use of chemical agents to block the nasal portal of entry of poliomyelitis virus has frequently been advocated. Schultz,<sup>69</sup> however, feels that this is impractical in man. This is due in part to the risk of inducing a permanent impairment of the sense of smell and partly because such an extensive injury must be induced in monkeys to afford protection.

**Treatment**—The advent of the *respirator* has made it possible to save many lives which would have been lost previously. Wilson<sup>70</sup> indicates that there is still considerable confusion concerning the indications for its use in poliomyelitis. It should not be used in cases of "bulbar" poliomyelitis, since the respiratory difficulty in such cases is due to obstruction along the airways, such as pharyngeal obstruction. Cases with shallow, irregular respirations due to

central disturbance of the respiratory mechanism are not benefited by the respirator, since in these cases the iron lung cannot overcome the shallow, jerky movements of the patient's chest.

In those cases, however, which show evidence of beginning paralysis of the intercostal or diaphragmatic musculature, the respirator should be used as soon as the paralysis is noticed. In this way much needed physiologic rest will be provided for the involved muscles, one must never wait until the paralysis is complete. Moreover, during the stage of recovery it is very important to see that the muscles have a rest each day in the respirator, thus ensuring a more complete recovery. The disadvantages of the respirator have been largely removed with the development of respirator rooms. At first there were objections to these rooms on the ground that individuals of different ages could not be subject to the same pressures, but these have been disproved.

During the *stage of recovery* the question is frequently raised as to when one should cease to expect further recovery and as a corollary of this when the orthopedic surgeon should take over. Seddon<sup>71</sup> outlined certain general rules in answer to these questions. First, if the patient has been under the proper care from the beginning, the greater part of recovery takes place before the close of the first year. *Rest in bed*, with

*splinting* as may be necessary, is most desirable throughout the period of recovery. If treatment has been inadequate, it is then best to consider the case as if it were a recent one, giving the patient the full benefit of the above treatment.

Next, if a limb remains completely paralyzed for 4 months, the paralysis is permanent and further treatment is a waste of time. Moreover, if no muscles are found to be completely paralyzed immediately after the acute phase, the prognosis is excellent and something approaching complete recovery may be expected. Involvement of the spinal and abdominal muscles often calls for more than the usual 6 to 12 months of *bed rest* required for paralysis of the lower limbs. Recovery sometimes continues for 18 to 24 months and any effort is worthwhile if a paralytic scoliosis can be avoided. The only certain method of following the progress of a case is to keep constant records. When recovery is maximal, treatment by *appliances* or *operation* has to be considered.

Geiger, Burlingame and Miller<sup>72</sup> studied the effect of injection of *convalescent serum* in 168 cases. Of these, 69 were treated cases and 99 controls. They conclude that convalescent serum is beneficial in the early stages of poliomyelitis, since there was a greater percentage of recovered cases without residual paralysis in their treated group.

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## POSTENCEPHALITIC PARKINSONISM

By BERNARD J. ALPERS, M.D., Sc.D.

**Treatment**—The symptomatic treatment of postencephalitic parkinsonism continues to engage the attention of many workers who are in search of an effective means of relieving both the tremor

and the rigidity of this disease. No cure has been found, but during the year a more effective drug treatment has been advocated, as well as an operative treatment in selected cases.



**Bulgarian Treatment**—As in the past, *belladonna* and *atropine* derivatives have been found to be most effective in controlling the symptoms of parkinsonism. In 1926 it was found that *wine extracts of Bulgarian belladonna* were unusually effective in the disease and its use has been sporadically advocated since then. In the past year have appeared some unusually good reports concerning its use. It has been found by practically all workers that the original white wine decoction of Bulgarian belladonna is unstable and the results obtained from its use variable. Tablets have been in use therefore to ensure stable preparations. Neal and Dillenberg<sup>73</sup> report on 100 cases treated over a 2-year period, all of them previously having had treatment with scopolamine, stramonium, amphetamine sulfate (benzedrine), or combinations of these drugs. The results obtained with Bulgarian belladonna were far superior to those obtained with any other form of symptomatic treatment. About one-third were greatly improved, one-half moderately improved, and the remainder slightly improved. A group of 23 cases treated with Bulgarian belladonna was compared with 21 treated with a synthetic preparation containing hyoscyamine 0.45 mg., atropine 0.037 mg., and scopolamine 0.012 mg. The results obtained with the Bulgarian belladonna were far superior to those with the synthetic preparation, as shown by an improvement in facial expression, decreased tension, and greater cheerfulness. Neal and Dillenberg believe that Bulgarian belladonna is the most beneficial drug available in the treatment of chronic encephalitis. They obtained their best results with a preparation known as *bellabulgra*.

Vollmer<sup>74</sup> has found that a synthetic compound of hyoscyamine, atropine, and

scopolamine was particularly effective in the treatment of parkinsonism. He found an empirical combination consisting of *hyoscyamine hydrobromide* 90.2 per cent, *atropine sulfate* 7.4 per cent, and *scopolamine hydrobromide* 2.4 per cent seemed particularly effective. This synthetic compound was found to be as effective as the natural extracts of belladonna roots. Treatment must be begun in small doses. The required dose varies from  $\frac{1}{2}$  to 7 tablets 3 times a day but ranges on the average from  $1\frac{1}{2}$  to 2 tablets 3 times daily. Slight dizziness, dryness of the throat and sluggishness are signs of overdose. General spirits and muscular rigidity respond first. Fifty-two patients were treated, 34 with postencephalitic parkinsonism and 18 nonencephalitic paralysis agitans. Fifty per cent of the postencephalitics and only 17 per cent of the nonencephalitics were markedly improved. There was moderate improvement in a further 32 and 33 per cent of the respective groups. Tremor does not respond as well as rigidity.

Eves<sup>75</sup> studied the effects of belladonna alkaloids containing the equivalent of the Bulgarian extract. Twenty-three patients were treated, 16 with chronic encephalitic parkinsonism, 5 with parkinsonism due to vascular disorders, and 2 with chronic encephalitis who were addicted to the use of scopolamine and did not co-operate. The vascular disorders responded poorly. In the encephalitic cases the rigidity decreased; tremor diminished in all the cases and in the majority was markedly improved. Oculogyric crises were diminished. Of 13 patients with chronic encephalitic parkinsonism 11 showed marked improvement, 1 slight improvement, and 1 no improvement.

Bulgarian belladonna has been used by some authors in the form of *rabellon*

with reported good results. Gayle<sup>76</sup> used this drug in dosages beginning with  $\frac{1}{4}$  tablet which was gradually increased by  $\frac{1}{4}$  tablet a day until a total of  $1\frac{1}{2}$  tablets was taken 3 times daily. Thirty-five patients were treated and all but 1 showed a slight to marked improvement. As in other forms of medication of this sort, dryness of the mouth and blurring of vision often developed as side symptoms. Draper<sup>77</sup> also used rabellon in 17 cases and reports good results.

**Synthetic Atropine**—Because of the many side effects of all the belladonna derivatives, and because many patients are unable to tolerate atropine in dosages large enough to give them relief from their symptoms, Schlezinger and Alpers<sup>78</sup> advocate the use of a synthetic atropine, particularly for cases which are sensitive to atropine. They used *syntropan* given in 3-grain (200 mg.) doses, starting with one 3-grain (200 mg.) tablet 3 times daily maintained for 4 to 5 days, then increased gradually by 1 tablet daily at 2 to 3-day intervals until a total dosage of 3 to 4 tablets 3 times daily was given (28 to 37 grains—1800 to 2400 mg.). Dosages of this size were well tolerated. Side effects such as vertigo and nausea were transitory. No dryness of the mouth or blurring of vision is experienced and the dose may be maintained for indefinite periods. Patients who do not tolerate the natural atropine tolerate the synthetic drug well. Rigidity is lessened in these cases, but tremor is not so much affected.

**Vitamins**—Jolliffe<sup>79</sup> has reported good results in postencephalitic parkinsonism by intravenous injections of vitamin B<sub>6</sub>. This vitamin was used because it appears to have some rôle in muscle metabolism. Jolliffe treated 15 cases of *paralysis agitans* all of which were bed-fast or chairfast, 10 of them for more than 3 years. All the patients received

$\frac{3}{4}$  to  $1\frac{1}{2}$  grains (50 to 100 mg) of *vitamin B<sub>6</sub> hydrochloride* intravenously daily or every other day. Of the 15 patients, 4 showed subjective and definite objective improvement. Two additional patients were subjectively improved. Jolliffe reports that "thus far objective beneficial results have been limited to lessening of rigidities and increase in strength in patients whose complete disability is of less than 3 years' duration, and who give no history of encephalitis."

**Operative Treatment**—Within the past few years operation has been attempted to relieve particularly the tremor in postencephalitic parkinsonism. *Rhizotomy* and *ganglionectomy* have been tried. More recently, parts of the motor cortex have been extirpated. Putnam sectioned the extrapyramidal tracts in the spinal cord in 5 cases without effect. In 2 cases of hemiparkinsonism *section of the pyramidal tract in the spinal cord* resulted in good improvement. In a brilliant study Meyers<sup>80</sup> reports on the use of operation in the control of parkinsonian tremor in 2 cases. In addition to *section of some of the extrapyramidal cortical areas*, Meyers *obliterated* in addition part of the *head of the caudate nucleus*. Of the 6 cases treated in this fashion by Meyers, 3 showed excellent results in control of the tremor, 2 were much improved, and 1 showed no effect.

Putnam<sup>81</sup> reports good results in the treatment of the tremor of paralysis agitans by *section of the motor fibers*. He reports 10 new cases of unilateral tremor, in 3 of which relief from the tremor of 1 hand was obtained by resection of the motor cortex at the anterior edge of the Betz cell region. Six patients were treated by section of the lateral pyramidal tract. In 2 of these cases only

a partial section of the pyramidal tract was performed; both patients obtained some improvement. In the other 4 cases the section was apparently complete. All 4 patients experienced substantial relief, usually with distinctly less disability than results from extirpation of the precentral gyrus. The final case obtained relief of unilateral tremor of the left arm and leg after section of the anterior limb of the internal capsule. The subsequent hemiparesis largely cleared up.

Putnam's conclusions concerning the relative merits of *cortical and pyramidal tract section* are as follows: "At present, the tentative conclusion seems

justified that tremor can be relieved by a cortical operation which does not wholly sacrifice the Betz cell area, and should therefore interfere only moderately with the use of the extremity involved. If such is the case, a cortical operation is probably to be preferred when tremor of the face, neck, or jaw is a serious consideration, or when the leg is not involved. Complete section of the lateral pyramidal tract is probably to be preferred if both the arm and leg are severely affected. It apparently produced less disability than even a restricted cortical operation in most of the cases in this series."

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## SPINAL CORD TUMORS

By BERNARD J. ALPERS, M.D., Sc.D.

### Herniation of Nucleus Pulposus—

During the past year attention has been called to the importance of herniation of the nucleus pulposus in the production of low back pain and sciatic pain. The entire problem of sciatic pain remains baffling in view of the multiplicity of its causes. A small group of cases due to a herniation of the nucleus pulposus has now been clarified as to symptomatology, but the results of treatment have not been clarified as yet because insufficient time has elapsed for a careful follow-up of operated cases. The syndrome is important in clarifying one of the many causes of sciatic pain, since practically all the cases of herniated nucleus pulposus have sciatic pain and all of them have low back pain.

Herniation of the nucleus pulposus in the lower lumbar region can be diagnosed in 50 per cent of cases from the clinical findings alone, according to Spurling and Grantham.<sup>82</sup> They stress

pain in the low back often associated with trauma or with lifting in a bent-forward position, or with sudden torsion of the trunk. This pain is relieved by recumbency and intensified by bending. It is accompanied by pain along the sciatic nerve. Stiffness of the lumbar spine, a positive straight leg-raising test, tenderness of the spinous process of the vertebra, muscle weakness, decreased or absent ankle jerk, and sensory changes in some instances complete the picture. An increased spinal fluid protein is usually present.

It is pointed out by Stookey<sup>83</sup> that herniation of the nucleus pulposus may occur in the cervical region. That an increase in the spinal fluid protein is not always present in the syndrome is shown by Macey,<sup>84</sup> who found that among 96 cases the average protein was only 53.8 mg., while in 36 cases it did not exceed 40 mg., and in 4 cases it was 45 mg. There is some question whether iodized

oil injection is necessary for the diagnosis of herniated nucleus pulposus. Spurling and Grantham believe the diagnosis is usually possible without it; others do not agree with this opinion. Hampton<sup>55</sup> has described the defects seen with oil myelography.

In over 500 operations for nucleus pulposus herniations Love and Walsh<sup>56</sup> have encountered only 5 recurrences.

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## OPHTHALMOLOGY

*Edited by* CONRAD BERENS, M.D.

### BLINDNESS

*By* B. FRANKLIN ROYER, M.D., Sc.D.

**Incidence**—Since the conservative statement was prepared some years ago "that there are more than 110,000 blind persons residing in the United States," much more information has become available. Co-operative Federal and State relief plans and State Pensions for the blind brought information about many heretofore unknown blind. Enough information is now available, on a more exact basis, to justify stating "that there are more than 200,000 blind residing in the United States," and when the files of all official relief and welfare agencies have been evaluated, the number may reach 250,000.

**Prevention**—Widespread use of the newer chemical preparations, *i. e.*, **sulf-anilamide**, **sulfapyradine** and **sulfathiazol**, in treating various acute pulmonic infections and gonococcic infec-

tions of the genital tract, seems to show quicker recoveries with fewer catastrophies than with older methods of treatment.

Ophthalmologists have given these chemicals extensive trial in acute ophthalmias of gonococcic and pneumococcic origin, both in infancy and adult life; they have been used also in the treatment of trachomatous eyes.

In the acute infections of the eye most favorable, sterilizing and healing results are being reported.

In the local treatment of trachoma, use of these remedies seems to kill the miscellaneous bacterial flora and to favor healing.

In so far as control of individual inflammatory conditions contributes to dissemination of infection, and so far as treatment lessens eye disasters, these

newer methods of treatment are a great contribution to prevention of blindness. When the full values and limitations of these chemicals are known still further prevention values may be found in their use.

The syphilis control programs so actively promoted by Federal, State, Municipal and private social agencies, and making available diagnostic laboratory procedures and treatment facilities all over America, will, as a byproduct, minimize the eye hazards of syphilis. Physicians in nearly all prenatal clinics and in private medical work secure prenatal blood tests for evidence of syphilis and,

where found, secure appropriate treatment of the expectant mother.

Many States are now by law requiring physical examinations and blood testing for all who seek marriage licenses, with provision for refusal of certification where evidence of transmissible disease is found. The health values of these legal requirements and newer medical practices should so lessen ophthalmia neonatorum and syphilitic eye disease in infancy, childhood and for the first 4 or 5 decades of life that the accomplishment should register definitely in the statistics of prevalence of blindness within 1 or 2 decades.

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## CATARACT

By ALFRED COWAN, M.D.

A great deal of literature has appeared on the subject of cataract, but how much new information it affords that will prove of practical value is difficult to estimate at the present time. Considerable experimental work is being done in order to gain additional knowledge concerning the etiology of *nutritional cataract*, particularly with regard to the effect of the action of the hormones on the metabolic changes produced by glandular function; and, while the information offered is mostly academic, it remains to be seen how much will prove to be of clinical value. Considerable animal experimentation is being done by numerous investigators who seem to agree generally that opacities of the lens are produced by faulty carbohydrate, lipid, calcium and/or vitamin B<sub>2</sub> and C metabolism, the effect being produced by changes in permeability of the lens.

The almost universal use of the slit lamp and corneal microscope has resulted in a much better conception of the various types of cataract. Meesmann<sup>1</sup>

arranges the total field of cataracts in the following manner: (1) Congenital cataracts; (2) contusion cataracts; (3) complicated cataracts, and (4) exogenous types of cataracts, *i. e.*, the diabetic, the tetanic, the myotonic (occurring with myotonic dystrophy), the syndermatotic (occurring with dermatologic disorders) and other endocrine types and, finally, the irradiation cataract.

Most ophthalmologists agree that senile exfoliation of the lens capsule, variously known as *capsular lenticular cataract* or *glaucoma, glaucoma capsularis*, etc., is entirely different from the condition known as *glassblowers' cataract*, in which there is a separation of the capsule of the lens. Senile changes in the lens are only a part of the senile changes that take place in the entire body.

**Surgery** remains the only cure for cataract, although many believe that some time in the future medicinal measures for the control of the cause, the delay and even the cure of cataract will be found.

## DISEASES OF THE CONJUNCTIVA

By S. HANFORD MCKEE, A B, M.D., C.M.

**Follicular Conjunctivitis**

**Treatment**—Drops of *mercury oxy-cyanide* 1/10,000 in saline solution often will be found to be very satisfactory in this type of conjunctivitis.

**Vernal Conjunctivitis**

**Treatment**—The question of therapy of vernal catarrh is rather a difficult matter. The use of radium, surgery, cauterization, and other similar drastic methods, has been generally given up. It is important to make the patient comfortable during the period of activity, and avoid irritating the eyes so far as possible. A mild *astringent solution* with the addition of some *vasoconstrictor* will afford these patients considerable relief during the seasonal attacks.

**Gonorrheal Conjunctivitis**

**Treatment**—*Sulfanilamide* was first recommended as a therapeutic agent in infections due to streptococcus hemolyticus of the beta type. Its use has, however, widened materially as reports from hospitals and in the general literature indicate its extensive use. In quite a number of cases now, sulfanilamide has proved to be of enormous value in the treatment of gonorrheal ophthalmia, either of the newborn or of the adult. The dosage has not yet been determined with sufficient accuracy, but it should be given in as large doses as possible. In adults a dose of 15 grains (1 Gm.), 4 times a day, for 4 or 5 days, has proved to be quite sufficient. It should be given, of course, with *sodium bicarbonate*.

**Ophthalmia Neonatorum**

**Treatment**—This is practically the same as has been prescribed for gonorrheal ophthalmia in adults, with the ex-

ception that the protection of the non-infected eye is not quite as feasible as in adults. In babies, too, the use of *sulfanilamide* is strongly recommended. While probably much must yet be learned about dosage, in these new drugs, 1 grain (0.06 Gm.) per pound weight in the 24 hours for a few days (4 to 5) will be found quite sufficient. Personal experience<sup>2</sup> has shown that the results obtained in gonorrheal infections of the eye with the use of sulfanilamide are remarkable.

**Inclusion Conjunctivitis**

**Treatment**—The course of inclusion conjunctivitis has been rather protracted, and methods of local treatment, especially in the adult, have been unsatisfactory. Recently, however, the administration of *sulfanilamide* has been advised, and in view of the marked curative effect which this drug has in trachoma, another inclusion disease, its use is highly recommended.

**Granular Conjunctivitis**

**Etiology**—It is now generally agreed that none of the bacteria which have been reported on the trachomatous conjunctiva is concerned etiologically with the disease. Many now believe that trachoma is caused by a filtrable virus contained in the elementary bodies of the trachoma inclusion. Recent writings are concerned chiefly with the relation of these inclusions to the rickettsiae.

**Treatment**—Recent reports by Loe,<sup>3</sup> Thygeson<sup>4</sup> and others, indicate that *sulfanilamide* exerts a very definite curative effect on a high percentage of active trachoma cases. It would seem that dosage and treatment time are very important factors. Adequate dosage has

been stressed by Richards, Foster and Thygeson,<sup>5</sup> and by Forster,<sup>6</sup> in which almost uniform healing was obtained on a daily dosage of  $\frac{1}{2}$  grain (0.03 Gm.) per pound continued for 3 weeks or longer. The drug appears to be most efficacious in the early cases, and should be used in relatively high dosage. Sulfanilamide causes rapid disappearance of the epithelial cell inclusions, characteristic of active trachoma. It does not seem to effect much the secondary bacterial infections so frequently seen in trachoma.

The following dosage is recommended:  $\frac{1}{3}$  grain (0.02 Gm.) of sulfanilamide per pound of body weight, every 24 hours, preferably scattered in fairly equal doses over 24 hours. It is tolerated better if given with equal amounts of *sodium bicarbonate*, and patients can take the drug better when confined to bed. This dosage is continued for 5 days, when the patient is given 3 days' rest; then follows another period of 5 days of the same dosage, followed by another 3 days' rest. The dosage is then reduced to  $\frac{1}{4}$  grain (0.016 Gm.) per pound of body weight for 24 hours, for 5 days. Then follows a rest of 3 days. Finally, the patient receives further treatment of the same dosage for 5 days.

Although the virus which is supposed to have caused trachoma is killed within a relatively short time, it should be

borne in mind that the follicles will persist until natural absorption takes place. This will require some 3 or 4 months. The total sulfanilamide concentration in the blood should not go above 7 to 10 mg. per 100 cc. of blood.

### Phlyctenular Conjunctivitis

**Treatment**—This should be conducted along 3 lines, *i. e.*, local, specific and general. If a cutaneous reaction to tuberculin is positive, a course of *tuberculin* should be instituted. In the hands of many, this has yielded good results. *General treatment* is most important and is instituted to raise the resistance of the individual.

### Allergic Conjunctivitis

**Treatment**—The treatment of all forms of simple allergic conjunctivitis is essentially the same; local treatment should be palliative only. The essential part of the treatment is to trace the exciting allergen and eliminate it. In the more acute manifestations of the disease, such as occur in hay-fever, local applications should be confined to soothing lotions, to which astringents of a very mild type may be added. *Acute exacerbations* may be relieved by vasoconstrictors, such as *adrenalin* or *cocaine*, but these should be used sparingly. In the chronic form, the same considerations apply.

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## DIPLOPIA

By JOHN N. EVANS, M.D.

The name "double vision" and ocular muscle dysfunction are practically synonymous, unless the disturbance arises in the perceptive structures of 1 eye only.

If patients are arranged in age groups, the groups will, of course, overlap and data, therefore, must be considered

from diverse studies before any conclusions are drawn.

Under the heading of prenatal influences, it is obvious that developmental defects can be placed anywhere in the muscle-nerve mechanism. Various intra-uterine infections ~~can~~ also be consid-



ered, most notable of which are syphilis and gonorrhea.

From birth to about the age of 5 years, special consideration must be given to those diseases which produce paralysis of the skeleton muscles and most prominent in this group will be found diphtheria and poliomyelitis.

Overlapping this group and the succeeding group to be considered, *i. e.*, those from 3 to 12 years of age, special consideration must be given to the muscular anomalies which appear associated with "farsightedness, defective sight in 1 eye (amblyopia exanopsia) and family history of strabismus." This is purely an ophthalmological disturbance and responds quite well to treatment if there is a minimum amount of delay.

Between the tenth and twentieth years it probably can be said that encephalitis lethargica should be placed first in consideration of the cause for double vision and particularly so if the images are vertically separated.

Between the second and fourth decades, double vision may have its origin in nasal accessory sinus disease and multiple sclerosis; but this period is very apt to include some of the etiological factors more commonly found in the next age group which extends from 30 to 60 years. In this group may be placed cerebrospinal syphilis, intracranial tumors and orbital lesions.

From 50 years on, the cerebral vascular accidents are apt to be met with as a cause for the muscle palsy and associated double vision.

Injuries must not be omitted from such a diagnostic list and would, of course, fall in any age period.

It should be kept in mind that such an age group is a simple arrangement which may be modified to meet varying conditions, but nevertheless is very helpful when elaborating a history in an effort to disclose obscure etiological factors.

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## EYE INJURIES

By CONRAD BERENS, M.D.

**Eye Injuries in War**—Shimkin<sup>7</sup> points out that the real destruction of the orbit and its contents is usually much more extensive than that indicated by examination of the external wound.

In treating cases of *cortical amaurosis* caused by a wound in the occipital region, he applied a *sterile dressing* and *removed bone splinters* and placed an *ice-bag on the occipital region of the head*. He believes that in severe occipital injuries, vision sometimes remains unimpaired when the brain substance of the visual cortex is lost; while the concussion of the occipital bone (the skull being intact) can produce an intracranial hemorrhage with a

moderate papilledema and also disturbance of the visual cortex, resulting in hemianopia of different grades and various central and paracentral scotomas, with great loss of vision.

In order to *differentiate between injuries and concussions of the cortical visual center and hysterical blindness* caused by severe traumatic neurosis with loss of vision, it is necessary to observe the patient's manner of bearing and whether or not he exhibits psychological symptoms.

Because modern firearms and bullets have greater velocity and more mass than before, their destructive action is also greater. When a bullet penetrates

the orbit, it acts by its force not only along the line of its path, but also develops immediately hydrodynamic forces in the fluid contents of the orbit; these forces act in all directions perpendicular to its path.

Since *sympathetic ophthalmitis* does not set in before the seventh day after the wounding of an eye, Shimkin does not advise immediate enucleation, for this time is sufficient for sending the patient to an eye surgeon.

Wounding of the *eyeball*, without injury to the orbit, is inflicted by artillery fire, bombs, gunshots and casual wounds. Shimkin states that these cases require *cutting away of the prolapsed iris*, covering the wound by a *conjunctival flap*, *removing the lens*, *extraction of a foreign body*, exact determination by means of x-rays of the location of intra-ocular foreign bodies, and magnet extraction. *Early operation* is likely to preserve the sight in twice as many cases as in late cases. A high percentage of cases lose their sight because of "indirect projectiles." The tiniest splinters, because of their enormous kinetic energy, tear through the cornea and the sclera. It is possible that eyeshields may partially protect the eyes against splinters during the explosion of bombs and grenades.

**Effects of Liquid Mustard Gas Upon the Eyes**—The studies of Livingston and Walker<sup>8</sup> on the effects of liquid mustard gas upon the eyes of rabbits reveal that irrigation with lotions that have a specific destructive effect upon the mustard is not recommended. *Sodium bicarbonate* (2 per cent) seems helpful and the dehydrating effect of *Bonnefon's solution* may be beneficial. The use of *atropine* against the irritation of the iris, leading to its contraction, is important. Antiseptic washes, *e. g., merthiolate* 1:10,000, are valuable

and are definitely indicated when secondary infection is present. *Oil drops*, especially cod-liver oil, *following irrigation*, apparently exert a favorable effect. Saturation of the system with *ascorbic acid*, given intravenously to 4 rabbits, had a remarkable effect in preventing the spread of keratitis and the progress of inflammation of the eyelids.

**Lens Lesions in Contusions**—Davidson<sup>9</sup> believes that the slit-lamp has furnished the ophthalmologist with a biomicroscopic technic of equal status with the technic of the histologist. The prognosis of contusion lens opacities occurring before the age of 30 years is good. After that age, he states that it should be guarded and the lesion not declared stationary until a 3-year period of observation has passed, in order to take care of statutes of limitation in the administration of workmen's compensation and protect the claimant against future deterioration.

**Lime Burns—Treatment**—Pether<sup>10</sup> showed that *ammonium chloride* was more effective than any solutions which have hitherto been generally employed to dissolve lime in the eye. He administered a 4 per cent solution in a series of cases with considerable success. First aid treatment should also include the preliminary application of an *analgesic solution* and mechanical *removal of large particles*.

**Treatment of Ocular Burns**—Zenkina<sup>11</sup> reports 3 cases of ocular burns, in which good results were obtained following the *transplantation of cadaver conjunctiva*; he states that results are better when the bed is more vascular. The pain abated the day after the transplantation of cadaver conjunctiva which was preserved at low temperature. After a time the transplant was absorbed. Zenkina believes that the transplant acts

as a local irritant and stimulates local regenerative processes.

**Corneal Injuries from Aniline Pencils — Treatment** — According to Sedan,<sup>12</sup> aniline pencils produce serious corneal injuries, usually resulting in loss of the eye. He reports 1 case which was successfully treated by *radical excision of the damaged tissue* and subsequent treatment of the cornea with applications of absolute *alcohol*. In his animal experiments with aniline-pencil injuries, the untreated eyes were lost; those treated with tannic acid or peroxide were scarred; but those treated with absolute alcohol responded fairly well.

**Corneal Damage by Novocain and Pontocaine**—Klar<sup>13</sup> reports 4 cases in which corneal damage followed overdoses of novocain (1 case) and pontocaine (3 cases) as local applications.

**Tetanus and the Prophylactic Use of Antitoxin Following Eye Injuries**—Avgushevich<sup>14</sup> stresses the importance of the routine administration of tetanus antitoxin instead of foreign proteins in ocular injuries. According to Cogan,<sup>15</sup> while a single prophylactic injection of 1500 units is probably adequate, repetition of this once during the first week is advisable as an added precaution.

**Removal of BB Shot with Giant Magnet**—McClelland<sup>16</sup> reports that BB shots are now made of steel and some are copper-plated. By means of a giant magnet he removed a BB shot which had lodged in the vitreous chamber, through the wound of entry. Normal vision was restored, the lens remained undamaged, and retinal detachment had not occurred 9 months after removal of the foreign body.

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## LOCALIZATION OF INTRAORBITAL AND INTRAOCULAR FOREIGN BODIES

By WILLIAM T. SHOEMAKER, M.D., and ROBERT M. LOWMAN, M.D.

**Historical**—Since the first conception of intraorbital and intraocular foreign body localization in the XIX Century, the problem has developed through evolutionary stages. The first attempt of localization of a foreign body was made by Williams in 1896, in which the foreign body was identified in relation to the bony orbit. Among the many investigators who followed Williams were Dahfield and Pohrt, de Schweinitz, Exner and others. While these men obtained partial success, Sweet in 1897 presented an ingenious original *geometric method* of localizing the foreign body in relationship to a fixed marker outside of the globe and to the surface of the cornea. The original instrument was modified and improved in 1909 and has remained one of the

most accurate and useful methods of localization. In 1902, Fox presented a *physiological method* of localization which depended upon the rotation of the eyeball between predetermined points of visual fixation and the resultant behavior of the foreign body in relationship to a specially built wire-frame in the conjunctival sac. In 1907, Bécère and Morax recommended a *stereoscopic method* of localization.

Supplementary methods for localization of foreign bodies in the orbit have also been introduced. These include the *injection of air* or *opaque media into Tenon's capsule* to delineate the posterior surface of the sclera; also visualization of the anterior hemisphere by a *bone-free projection* after the method of Vogt. In

addition, Pirie's method of *autolocalization* is employed. In this method, the patient attempts to identify and check the localization of the foreign body by the sensitivity of his retina to the roentgen rays. Attempts to localize the particles with reference to various markers introduced into the conjunctival sac have also been devised. Pfeiffer in 1940 devised an apparatus in which he employed a *Zeiss contact lens* adapted for localization use by Comberg in 1927.

**Methods**—Because of the position of the globe in relationship to the orbit and the complicating superimposed bony structures of the face producing a complexity of shadow densities, the use of specially built mechanical aids for location of ocular foreign bodies is a necessity. Most of the methods for localization are complicated, require considerable instrumentation and have definite limitations. The charting results are based on geometric calculation and triangulations, and a small error in technic and adjustment is registered as a large error on the chart. By means of localization and charting, the following points regarding an intraorbital foreign body may be obtained: (a) Visibility of the foreign particle and its approximate size; (b) whether it is intra or extra-ocular and its relationship to the structure of the orbit and globe.

An understanding of the underlying principles employed in the *geometric method* of localization of an intraorbital foreign body is essential to an understanding of eye localization. The methods and principles of the *modified Sweet procedure* are usually chosen to illustrate the geometric method, although the features are applicable to any method in which the eye remains stationary during the examination. The mechanical design of the modified Sweet apparatus maintains a constant tube target, film distance, a

constant inclination of the roentgen-ray beam and a constant shift of the tube which permits the formation of a known parallax angle. It is then possible to determine the position of a foreign body in relationship to the metallic marker and calculate the position of the particle to the optic center. The positioning of the metallic marker—a steel ball mounted in a celluloid ring directly in the line of the optic axis opposite the center and exactly 10 mm. anterior to the tangential plane of the cornea—is made possible by adjustable screws, a telescope and a reflecting mirror. Sighting through a telescope, the instrument can be adjusted until the mirror shows the image of a cross wire directly in contact with the summit of the cornea. Films are then made, which permit measurement of the position of the foreign body posterior to the marker and the distance above or below the horizontal plane. On another portion of the same film, protected during the previous exposure, another view is made after the x-ray tube has been shifted a predetermined distance parallel to the film surface. This parallel shift forms 2 series of similar triangles in which the metallic marker is the apex in one series, and the foreign body is the apex in the other. Since in the similar triangles the corresponding sides are proportional, it is possible to calculate the distance of the foreign body to the film surface and also to determine the position of the foreign particles in the sagittal plane.

These findings are charted on a diagram whose factors reconstruct the actual operating conditions of the Sweet apparatus. Measurements made from the x-ray film are indicated on a chart corrected for the magnified distortion. By employing the Sweet apparatus for localization under definitely known conditions, the recording of these results is

done by reversing these conditions in charting the measurements obtained by the procedure. A key plate is employed as a convenient and accurate means of transferring the measurements obtained on the film, to a chart.

The practical use of localization is limited to metallic foreign bodies. The x-ray density of the image of the foreign particle is directly proportional to the specific gravity of the material examined. While every substance has its index of transparency, the index of all *nonmetallic substances* that can ordinarily enter the eye is too high for satisfactory shadowing. The metals have a low transparency for the x-ray and therefore cast distinct and definite shadows. The density of the surrounding orbital tissues, especially of the eye, is another factor reducing contrast and preventing adequate formation of a demonstrable image of non-metallic substances. Spackman collected samples of materials which had been found to act as intraocular foreign bodies. Under especially reproduced conditions, using a dried skull, wax and an enucleated eye in which the particles were imbedded, data were obtained which gave the approximate size which a foreign body of a specific density must be, to be detected by the usual methods of localization, and also by the bone-free projection method. Possible sources of error were inherent in the apparatus and in the inability of the patient to maintain ocular fixation because of nervousness, pain, cataract or hemorrhage.

Depending upon the location of the foreign body in the globe, the accuracy of the modified Sweet method is estimated by various observers to be within 2 to 4 mm. Because the position of the foreign body when it is situated in the anterior chamber is nearer to the indicator ball, the Sweet method is most accurate in these cases, because the error

from distortion is less. Even though the foreign body may appear to be within the globe as charted, caution must be exercised in the interpretation of the position of foreign bodies which appear to lie in close relation to the posterior border of the sclera. While the foreign body may appear within the model globe in the diagrammatic eye on the charts, it may actually lie outside of the globe, and it may be necessary to resort to accessory methods to determine whether the foreign body is intra or extraocular. In the modified Sweet method charts, the foreign body is localized in reference to a model eye of 24 mm. Since the actual eye may be larger or smaller than the model eye, the position on the chart does not necessarily indicate the position of the foreign particle within the patient's eye. Spackman analyzed a series of 100 cases and showed that a tendency existed for the larger particles to lodge in the posterior hemisphere or to perforate through the globe. For this reason, it is important to determine the position of the foreign body in relation to the scleral boundary.

Another example of a geometric foreign body localization is the *procedure* described by *Pfeiffer*. Adapting the Zeiss contact lens previously devised by Comberg, Pfeiffer has described a unique method of localization. The contact lens of Comberg has the limbus of the cornea designated by lead markers. An average size lens, having a scleral curve of 12 (12 mm. radius) and a corneal curve of 8 (8 mm. radius), is used. Inserted and removed with ease, it may be used, after sterilization, without difficulty on a lacerated globe. Pfeiffer has introduced an L-shaped arrangement of tunnels to permit placing the patient's head in 1 position for the 2 exposures. By this means, only the tube is shifted then for the different exposures. The injured eye

is anesthetized with 5 per cent *solution of pontocaine* and the contact lens is inserted. After the proper position has been found by the glass, the head is immobilized and 2 exposures are made, a posteroanterior and a lateral. The x-ray beam is directed perpendicular to the tunnel surfaces so that the x-rays pass through the eye in which the foreign particle is present. The contact glass may be rotated through the tunnel openings to place the lead markers in the vertical and horizontal planes. Films then are made in the necessary positions. To plot the position of the foreign body, a reference line is drawn through the superior margins of both orbits. A line is drawn to bisect the foreign body and pass through the center of the lens. This angle is measured with a protractor and plotted on the chart. Perpendiculars and similar measurements are used in the lateral view and these measurements are also charted.

If the foreign body lies near the scleral boundary anteriorly, a thorough search of the eyelids and conjunctiva and soft tissues of the globe should be done to determine whether or not the foreign body is extraocular. In the posterior boundaries, the question of *double perforation* arises and considerable more difficulty is encountered. Stephenson attempts to determine the position of the foreign body and check it with reference to the circumference of the eye in the plane in which the foreign body is situated. This investigator measures the diameter of the eyeball in the actual plane of the foreign body. Using half of this measurement as the radius, a circle is drawn on each of the diagrammatic planes on the Sweet chart. Measurements by *Stephenson's method* are transferred from 1 projection to either of the other projected diagrams. If the foreign body lies beyond the limits of the circle

constructed from the plane in which the foreign body lies, it is outside the limits of the model eye and is probably extraocular. A mathematical check to determine whether or not the foreign particle is extraocular is also possible. From the charts, the distance the particle lies from the equatorial planes can be determined. By means of a rectangle constructed so that the optic center is the point of reference, the spatial relationship of the foreign particle to the 3 equatorial planes is determined. If the sum of the squares of the distances of the foreign body from the optic center along each of the equatorial planes is more than the square of the radius of the model eye, the particle is extraocular (the radius of the model eye is 12 mm.).

To determine the *anatomic relationships* of the foreign particle to the eye of the patient, such procedures as *bone-free radiography* of the anterior hemisphere and the parallax methods are used. The bone-free projection of the anterior chamber is used when the particle is thought to be in the area but is not seen by ophthalmoscopic or slit-lamp examination. A dental film is bent and slipped between the eyelid and the bony orbital margin and it is then exposed. Often the dental film may be placed horizontally below the globe. The roentgen-ray beam then is directed through the top of the skull and the object identified from two 90° angles. By means of a beam of soft radiation directed at the film at a 90° angle, the cornea and the anterior portion of the globe between the open lids is shown. The lids are opened as widely as possible. Particles that are small or that have a low specific gravity may be recognized by this means.

The rotation of the eye in the *parallax method* becomes the factor of importance in determining whether the particle is intra- or extraocular. Thus, in this

method, when the eye is rotated between predetermined external points of visual fixation, the intraocular foreign body will be rotated about the optic center. The patient's head is immobilized with the sagittal plane parallel to the film and the injured eye nearest the film. The patient is instructed to raise both eyes, although the position of the head is not changed, and the first exposure is made. The patient gazes at a horizontal point and a second exposure is made and, finally, the eyes are turned downward for the third exposure. Some workers make all 3 exposures on a single film. Others use separate films and superimpose them after being processed. If ordinates drawn from lines connecting the 3 images of the foreign particle cross at the optical center of the globe, the foreign body is regarded as being within the globe. If the ordinates cross at points other than the optic center within or outside of the globe, the particle is extraocular. In most cases of extraocular particles, movement may be so slight that no doubt as to the position of the particle will exist. If, however, the particle is imbedded posteriorly in Tenon's capsule or adheres to the posterior segment of sclera, it may behave under the procedure described as if it were intraocular. Again, a particle may be situated in the fluid vitreous and act as if it were extraocular. For this reason, various methods supplementary to the standard geometric procedures must be employed.

In addition to the methods described, it is necessary that the operating ophthalmologist be acquainted with the problems associated with the *roentgen examination* following extraction or attempted extraction of a foreign particle. It is often necessary to make check-up localizations to determine how far a particle has been displaced if the operator has not been able to remove the foreign

body. The operator will usually try to extract the foreign particle through the wound of entrance if the body is responsive to the *magnet*. Many operators will attempt a single trial with the magnet and return the patient for relocalization. If the particle is imbedded and no movement is demonstrated, no further attempts with the magnet are made. Attempts to remove the particle by *blind searching* or by *biplane fluoroscopic control* may be resorted to.

In the particle which appears to be buried in the posterior sclera, the question of *double perforation* arises. In these instances, the injection of air into the capsule of Tenon and autolocalization are employed to settle the question, if the previously described procedures are found wanting. Lipiodol, diodrast and other opaque media have been used for injection into the space, but these tend to prevent clear visualization of the particle. By means of *air injection*, a distinct zone of contrast is produced outlining the posterior and outer surface of the sclera. (Gasteiger-Grauer). Modified and improved by Spackman, the method is thus described: After thoroughly anesthetizing the eye, the patient is instructed to turn it downward and inward. A point about midway between the superior oblique and external rectus is located and the conjunctiva grasped, using sterile precautions. A curved cannula is then inserted below the conjunctiva and the needle carried between the conjunctiva and Tenon's capsule for a few millimeters before puncturing the capsule. If a straight cannula is used, the air will leak back below the conjunctiva and into the retrobulbar tissue. An attempt is made to inject 10 cc. of air, but in the writer's cases, 6 to 8 cc. were sufficient. When the eye is proptosed, due to air posterior to the globe, and increased resistance is felt on the

piston of the syringe, the injection is discontinued. The proptosis must be apparent, and this is the best guide as to the correctness of the procedure. If the conjunctiva bulges forward, the needle is not within the space of Tenon or there is too much leakage. In this case, the test is of no value. The radiographs are made at leisure, preferably from several angles, as it is important to separate the shadow of the foreign body from that of the space of Tenon. The layer of air below Tenon's capsule forms a band which may be plainly visualized in contrast to the denser bony tissue of the orbit and by making films from various angles, the relation of the particle to the capsule may be accurately demonstrated. In actual practice, the question of double perforation must be considered in approximately 5 per cent of the cases. In Spackman series of 100 cases, a question of double perforation arose in almost 30 per cent. Air injection may be impossible because of adhesions or fusion between the capsular layers.

Taft and Pirie have utilized the principle of the visibility of the *x-rays* without the use of the fluoroscopic screen. Following complete dark adaptation, the patient is placed before an x-ray tube in a darkened room and questioned whether he can observe a black spot in the beam of fluorescent light which is visible when the tube is active. A diagram of the relation of the black spot to the cross wires of a frame placed be-

fore the injured eye, is then made by the patient. This will be placed in the quadrant diametrically opposite that in which it is actually situated.

The lens produces no inversion of the image in this case, but its situation is interpreted as though it were reversed because of the reaction of the brain centers. For example, a patient will place a foreign body as being in the upper outer quadrant when it is actually situated in the lower inner quadrant. In cases where the retina has been perforated, no response can be obtained by this means and this method is used to determine whether the foreign particle lies anterior or posterior to the retina. Pirie also feels that the damage to the retina may also be recognized by this means. This procedure is also recommended for determining the presence of *glass in the eye*. The fluorescence of the glass after x-rays have passed through the eye may be recognized by a well adapted ophthalmologist in a darkened room.

It must be strongly advised against complete dependence on any single routine practice to determine whether or not double perforation is present. In addition, it is to be remembered that the accuracy of results in the localization of any foreign body is strictly controlled by the accuracy in applying the method. Each method of localization has definite limitations and the roentgenologist must recognize this fact and not be led astray.

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## HEMIANOPSIA

By JOHN N. EVANS, M.D.

In interpreting these half-field defects, it is not enough to keep in mind the mental picture of the gross anatomic visual pathway, but it is necessary also

that the nerve fiber bundles, their relations to each other and to adjacent structures be visualized. Defects arising from disturbances of the fiber mechanism



are called *neuroscotomas* and the technic of mapping them is called *neuroscotometry*.

Sometimes these defects are modified by another type of field defect which

arises from disturbances of the intracranial pressure or the blood circulatory system; these defects are called *angioscotomas* and are studied by a technic called *angioscotometry*.<sup>17</sup>

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## DISORDERS OF THE IRIS, CILIARY BODY AND CHOROID

By JOHN N. EVANS, M.D.

**Treatment**—In the treatment of uveal disease, the last few years have provided the ophthalmologist with a new agent in the form of *sulfanilamide* and its derivatives. Since the uveal tract is most likely to be affected from a systemic infection or focus, the medicament is in this sense directed to the primary cause.

In spite of the remarkable results obtained in certain general and ocular diseases, there is as yet, inadequate material in the literature from which to evaluate its relative effect in uveal tract disease. Its position is much more secure for instance in the treatment of conjunctivitis.<sup>18</sup>

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## MYOPIA

By WILLIS S. KNIGHTON, M.D.

Within recent years the study of myopia has shifted the emphasis from the mechanistic approach—elongation of the globe—to the biological. The fact that myopia of low or moderate degree may exist without elongation of the globe, whereas axial elongation plays a predominant rôle in high myopia, emphasizes the view that myopia is to be divided into separate types. Typical myopic fundus lesions are usually associated with axial elongation, but they may exist in short eyeballs, and they may be entirely absent in elongated eyes. It appears then that fundus lesions and axial elongation are dissociated phenomena which frequently, but not necessarily, are coupled genetically. A clinical

method for measuring axial elongation of the globe in life, would help immeasurably.<sup>19</sup>

The total refractive error of the eye is made up of several variable components, such as axial length and resistance, curvature of cornea and lens, refractive index of media, etc. Many of these are undoubtedly conditioned by heredity and await a better understanding of the subject before myopia can be understood. Rational treatment must come later.<sup>20</sup>

Progressive myopia of the malignant type is rare. It is an independent biological group. Its management and treatment are individual problems.

## OPTIC NERVE AND RETINA

By ARTHUR J. BEDELL, M.D.

### Papilledema, Choked Disc

This most commonly results from increased intracranial pressure caused by excess fluid, abscess, or tumor. It may come from orbital disease, sinusitis or reduced intraocular pressure. Recently a number of cases has been reported where a most careful examination failed to disclose any intracranial pressure or other cause. In papilledema of this type there is frequently a hemorrhage in the fundus on the swollen disc or remote therefrom, a moderate headache, rarely as severe as that which is usually associated with brain tumor, although it is to be remembered that a brain tumor may be very large without any headache. It is commonest in the second decade of life. Women seem to be afflicted 3 times as often as men. It may recur after seeming recovery.

This type of papilledema may be unilateral or bilateral, associated with little visual disturbance, or be the first sign of a serious condition which progresses, causing loss of vision and marked neurological symptoms. The majority of these cases are cured, although occasionally permanent blindness results.

*Treatment* can only be outlined after a complete ophthalmological and neurological study. When in any papilledema it is found there is no evidence of brain involvement, the brain should not be operated upon. The diagnosis calls for great skill and experience in determining the proper procedure to follow.<sup>21</sup>

### Retrobulbar Neuritis

**Etiology**—This condition has been proved to be associated with vitamin deficiencies, such as pellagra and pernicious anemia.

### Tumors of the Optic Nerve

These tumors may be confined to the nerve or be part of a general condition, such as von Recklinghausen's disease.<sup>22</sup>

### Traumatic Retinal Angiopathy

In this condition, which follows a direct head injury, compression of the chest or fracture of the lumbar vertebrae, there is a characteristic fundus appearance of great, white, fluffy clouds with retinal hemorrhages. The edema disappears and optic atrophy, either partial or complete, follows.<sup>23</sup>

### Syphilitic Optic Atrophy

**Treatment** of syphilitic optic atrophy which has been notoriously inefficient, seems to be more efficacious when *vitamins* are given at the same time the *specific treatment* is administered.

### Retinal Arteriolar Sclerosis

This term is now used to indicate the involvement of the smaller retinal vessels in contrast to the former general term arteriosclerosis.

### Thrombosis of the Central Retinal Vein

This condition may end in 1 of 3 ways, *i. e.*, secondary glaucoma, organization of the exudate, or complete resolution with a return of function.

### Demyelinating Diseases of the Nervous System

These may be ushered in with an acute optic neuritis. There are 4 distinct types, *i. e.*, disseminated sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica, and encephalitis periaxialis diffusa. The pathological changes may

be confined to the optic nerve, optic nerve and spinal cord, or be generalized such as is found in multiple sclerosis.

Diagnosis and treatment call for a complete understanding of the multiform expressions of each form.<sup>24</sup>

## REFRACTION

By CONRAD BERENS, M.D.

Van Wien<sup>25</sup> has described the *Leland refractor*, which utilizes polarized light. This instrument provides a sensitive test for the axis and amount of astigmatism, permits a balancing of the spherical cor-

rection and adjustment of the axis of the cylinders in binocular vision. In cases of muscular imbalance, the spherical changes required or the proper amount of prisms, if necessary, are indicated.

## STRABISMUS AND ORTHOPTIC TRAINING

By CONRAD BERENS, M.D.

### Abnormal Retinal Correspondence

—According to Burri,<sup>26</sup> the classic assumption that the 2 retinas correspond exactly by either a cell or a retina to cortical area relationship has no neurologic proof so far beyond the discovery of a certain topographic arrangement of the retina in the cortical centers. Burri believes that knowledge points toward a dynamic plasticity rather than toward a static anatomic relationship.

In a study made at the New York Eye and Ear Infirmary, preoperatively abnormal retinal correspondence was present in 61 per cent of 227 patients who received no preoperative orthoptic training; normal retinal correspondence was established before operation in 75 per cent of the 73 patients who received preoperative orthoptic training. After surgery, anomalous retinal correspondence persisted in 55 per cent of the 80 patients receiving no postoperative orthoptic training but in the 183 patients receiving orthoptic training postoperatively, 81.5 per cent had normal retinal correspondence.

### Orthoptic Training

—The increasing use of orthoptic technicians is doing much to advance the orthoptic treatment of squint because the ophthalmologist is unable to devote the needed time to this work.

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## OTORHINOLARYNGOLOGY

*Edited by* FRANCIS L. LEDERER, B.S., M.D.

### DISORDERS OF THE EAR

*By* FRANCIS L. LEDERER, B.S., M.D.

#### Deafness

**Research**—The next step in auditory research is discussed by Kobrak, Lindsay and Perlman,<sup>1</sup> *i. e.*, the value of animal experimentation in the study of the function of the inner ear. The acoustic reflex contraction of the intrinsic muscles of middle ear is a simple, reliable indicator of cochlear function in animals and in man. The conduction of the sound in the inner ear is studied. It is demonstrated that sound may reach the cochlea through the air of the middle ear, enter it through the window and be conducted through the scala tympani ("Reversed sound conduction in the cochlea"). The intralabyrinthine fluid is an essential conductor of acoustic energy. Disturbance of the cochlear fluid is incompatible with good function. Direct conveyance of acoustic energy through the nose to the nerve-ending is not possible. Regardless of the portal through which sound enters the cochlea, the intralabyrinthine fluid is "the first common path" of sound conduction.

**Etiology**—Diseases of bones, such as senile osteoporosis, osteomalacia, athyreopituitary dwarfism, otosclerosis (rare forms), osteitis fibrosa and deformans,

chondrodystrophy and osteogenesis imperfecta often have been associated with disturbances of the ear. Brittle bones associated with deafness and blue scleras is discussed by Fox and Sweet.<sup>2</sup> The history and findings of the cases of 2 persons in 1 family, a brother and sister, having the interesting lineal syndrome of brittle bones, blue scleras, and deafness, are presented. The hereditary characteristics of the condition and the pictures of blue sclera, brittle bones, dislocations, and deafness are discussed. (Follows Mendelian Law.) The blue sclera and brittle bones are noticeable early in life, the deafness, which is of the otosclerotic type, usually comes on in the late twenties.

The pathogenesis of otosclerosis and its various theories are discussed by Sparer.<sup>3</sup> The author himself believes that it is possible, on an anatomic basis, to account for vasomotor imbalance in the distribution of the fibers of the tympanic plexus which control the blood-vessels of the middle ear—with its cause, a pathologic condition in the nasal sinuses, influencing it through the sphenopalatine ganglion. Also, the histopathology in otosclerosis can be accounted for on the

same basis as in sinusitis—bone changes being due to alteration in local circulation, which is due to a vasomotor imbalance in the sympatho-parasympathetic nerves controlling these blood-vessels. If the syndrome of otosclerosis is dependent on these factors, it should supply a rationale for a new avenue of approach in the presentation and treatment of this condition.

A comprehensive review of the subject of chronic progressive deafness, including otosclerosis and diseases of the inner ear, is presented by Shambaugh.<sup>4</sup> The same author<sup>5</sup> discusses *dipacusis* as a localizing symptom of disease of the organ of Corti. He offers some theoretic considerations based on clinical observations and suggests a practical application of the sign.

1. Dipacusis is due to a lesion of the organ of Corti.
2. Dipacusis is a more frequent symptom than is generally appreciated, but to be detected, it must be tested for specifically.
3. The test for dipacusis is simple, quick and reliable. It is best done with tuning forks.
4. Dipacusis occurs in the following clinical conditions:
  - (a) Otosclerosis with labyrinthine involvement.
  - (b) Acute serous labyrinthitis secondary to acute or chronic suppurative otitis media.
  - (c) Operative trauma to membranous labyrinth.
  - (d) Hemorrhage into the labyrinth.
  - (e) Acoustic trauma to the labyrinth.
  - (f) Labyrinthitis resulting from focal infection.
  - (g) Labyrinthitis due to allergy.
5. Dipacusis is found in most cases of Ménière's disease with defective hearing.
6. Ménière's disease is due to nonsuppurative labyrinthitis, sometimes allergic, sometimes the result of focal infection. There may be vertigo without deafness, vertigo and deafness or deafness with-

out vertigo, according to whether the entire membranous labyrinth or only a portion is involved.

- 7 Perception deafness due to a lesion of the membranous labyrinth is characterized by the following conditions:

- (a) Hearing for low tones is impaired as frequently as for high tones.
- (b) Dipacusis is present.
- (c) Vertigo is present
- (d) In many cases the pathologic lesion is reversible, at least in early stages, so that hearing is subject to marked fluctuation, and it may return to normal.

### Diagnosis of Congenital Deafness

—Authorities are agreed that the diagnosis of congenital deafness in infants is not easy. There are few tests that can be applied accurately in the case of a child less than 3 years of age.

A deaf child cries but is said not to cry as loudly as a normal one. Tests, such as clapping the hands, slamming doors, and the like, are not reliable, since they introduce too great an element of vibration and tactile sense.

A few observers have studied the conditioned reflex method of determining the presence and nature of hearing in infants, but this is obviously a painstaking, time-consuming and not easily available method. The most practical tests consist in eliciting the various *oculopalpebral reflexes* in response to loudly struck *tuning forks*, especially of a pitch of 4096 double vibrations. The examiner stands behind the child so that his movements are concealed and another observer watches for blinking of the lids and dilatation of the pupils. This test is highly thought of by clinicians, for if an individual hears the C-4 fork, there cannot be much impairment of the perceptive apparatus. This response is coupled with other acoustic motor reactions producing a so-called startle pat-

tern, the whole reaction forming a reliable indicator of ability to hear.

Congenitally deaf individuals furthermore, as a rule, have normal labyrinth function, whereas the reverse is often true for persons profoundly deaf because of some inflammatory process.

In older children co-operation in testing permits the use of tuning forks, the audiometer and similar methods. It is thus possible to determine the degree of deafness and the presence or absence of remnants of hearing, important in the training and education of the child. It is said that most individuals congenitally deaf are not completely so, but possess tone islands and gaps.

Tuning forks and audiometers, not being available for use in the very young, observation over a period of days plays a large part in diagnosis. It is important, furthermore, to rule out the possible though rare instance of primary mutism with good hearing, but much more is it necessary to rule out mental deficiencies which interfere with proper progress and simulate the delay in speaking seen in the deafened. The services of a child psychiatrist are advisable in such situations. *Treatment* is given through education by special methods in special schools. *Lip reading* is started early as is the so-called *acoustic method*.

**Deaf-mutism and Pigment Degeneration**—Weber<sup>6</sup> discusses the question of the combined appearance of degeneration of the pigment of the retina with deaf-mutism being due to an internal causal connection or to hereditary anomalies existing side by side. A family in which pigment degeneration and deaf-mutism concurred was studied. The genealogic tree of the family failed to furnish an answer to the question of how the combined 2 disorders were to be explained. It is noteworthy that the sib-

lings who are affected suffer from the 2 disorders simultaneously. This combined appearance creates an impression that the 2 defects belong together, the more so since in the 3 cases in which the defects occurred the vestibular nerve did not respond to stimulation. The assumption of the common origin of the 2 hereditary disorders is contradicted, however, by the fact that the pigment degeneration of the retina has been known to concur not only with the recessive deaf-mutism, but also with the dominant hardness of hearing of the inner ear.

The combination of deaf-mutism with pigment degeneration has raised the question of whether it is due to a hereditary combination elicited by a common gene. The opinions on this subject are contradictory. The author reviews the factors cited in favor of a unitaristic origin as well as those favoring a separate and independent hereditary transmission. Indicative of an independent hereditary transmission are the essential differences of deaf-mutism and pigment degeneration; the fact that in most instances the 2 disorders appear separately and that the combination is the exception; the promotion of the combination by blood relationship of the parents; the concurrence of feeble-mindedness with one or the other or with both of the defects and the occurrence of other combinations. The author feels, nevertheless, that the acceptance of an independent and separate hereditary transmission must be made with reservations, because the examined material is insufficient to permit a complete survey of the problem. The final answer will probably be similar to that given by Siemens, *i. e.*, that the apparent correlation of recessive hereditary defects in the children of parents related by blood is due to identical descent, because, since all reces-

sive defects are more frequent with inbreeding, it is self-evident that they frequently concur among siblings or even in the same person.

**Functional Examination**—In covering the recent literature no new tests are found or practical variations of the standardized methods now in vogue. *Audiometry* is used more widely in this Country as well as abroad. Interest is being manifested to a greater degree in the problem of the child of school age. In a symposium on the recognition, treatment, and prevention of hearing impairment in children, Crowe<sup>7</sup> and his associates<sup>8</sup> report the results of a study of 1365 Baltimore school children ranging from 8 to 14 years of age. Crowe stresses the following points:

1. The recurrence of adenoids after operation on young children is so common that it must be regarded as normal.
2. This recurrent lymphoid tissue may impair the function of the eustachian tubes, cause a low grade serous inflammation, and lead to a chronic progressive deafness
3. Recurrent or hyperplastic nodules of adenoid tissue in and around the pharyngeal orifice of the eustachian tubes are so located that they cannot be removed surgically but irradiation (with radon applicators) is recommended to reduce the size of the hyperplasia.
4. Radiation is used solely for the hyperplasia, thus reducing the obstructing tissue to secure proper ventilation of the tubes. The treatment is advised before irreparable damage has been attained.

It is the opinion of Crowe and his associates that the prevention of impaired hearing in school children is clearly a problem of such magnitude that the co-operation of otologists, family physicians, public health agencies and school authorities will be needed for its successful practical solution. Theirs

were random tests made on school children by means of the audiometer, supplemented by tuning forks. They found 2.8 per cent of children with 1 or both ears affected. These cases are being very carefully studied, controlled and treated, and over a period of years will be of considerable interest.

**Hearing Tests**—Some practical considerations with regard to *hearing tests* is given by Wells,<sup>9</sup> who says that hearing tests of the diagnostic kind are obviously the province of the ear specialist and it seems advisable that the instrument particularly designed for this purpose be kept in his hands. However, the physician should not fail to recognize that simple acuity hearing tests may very well be made by the layman and, considering the great number of such examinations that have to be made, this is the practical course. Accordingly, Wells suggests an electrically operated unitorial instrument of the watch-tick type as suitable for this purpose. He believes for reasons stated that the interrupted 1000 cycle tone will give a fairly representative estimate of conversation hearing. The intensity changes must be as accurately calibrated as in the best of audiometers. Practical requirements will be served best if the dial readings will be in percentages of normal. After all, it must be admitted that absolute precision in hearing tests is an unattainable ideal in spite of instrumental precision. The personal factors, although they receive relatively little attention, are of much greater influence than usually realized. Since they are concerned with psychic phenomena, they cannot be accurately calculated and controlled. It is believed, however, that a better knowledge of the principles involved and stricter observance of them in practice would materially help in cutting down the usual margin of error.

**Treatment**—Much of the activity in the treatment of deafness has been directed toward the alleviation of chronic progressive deafness. The estimation of improvement in hearing following therapy is discussed by Hughson and Witting.<sup>10</sup> In an effort to establish some standard whereby different observers may compare the results of their therapeutic efforts in the management of deafness, certain standards of measurement have been suggested. There will, of course, be differences of opinion in regard to the routine merits of individual tests. It is felt, however, that for a completely accurate appraisal, the routine suggested will eliminate any criticism of reported results.

The recently awakened enthusiasm for new forms of treatment in deafness, whether medical or surgical, demands that all results be most rigidly analyzed and that there be a common standard of interruption.

*Bone conduction audiograms* and *loudness balance tests* are essential in the selection of cases for certain types of surgery. This rather general feeling that thresholds of hearing for individual frequencies do not represent the actual hearing level for speech intelligibility is doubtless entirely sound. The routine employment, therefore, of some type of *intelligibility test* would seem to answer the objection to the standard threshold audiogram.

Of even greater importance is correlation between a minimum standard of improvement and expected variation in *repeated audiograms*. It should be emphasized also that only by frequently repeated audiograms can any real conception of the effect of therapy be gained, and also that practical recordings are of value only if they are derived from a considerable series of audiograms.

The arbitrary figure of 10 decibels has been chosen as the minimum improvement of any real consequence to be considered and this only if the test is carried on under the best conditions.

In recent literature there has been a great deal of material presented to show the value of *vitamin therapy* in the treatment of *chronic progressive deafness*. A further contribution to this subject by one of the main proponents of this form of therapy is presented by Selfridge,<sup>11</sup> who discusses the rôle of estrogenic substances. He offers the following points:

(1) Estrogenic substances probably play an important rôle in conduction deafness. *Estrogen* relieves completely in many cases the tinnitus, menstrual irregularities, and other symptoms occurring during menstruation. Unfortunately, these symptoms recur in many instances when estrogen is discontinued.

(2) There is definite evidence that *thyroid* is of importance and also the *pituitary* and *adrenal cortex* in treatment of deafness.

(3) *Thiamin chloride* and *nicotinic acid* are exceedingly helpful as may be other factors of the *B<sub>2</sub> complex* and other vitamins.

(4) Neither nerve nor conduction deafness are caused by any single factor, but appear to be linked with the various factors related to growth, *i. e.*, endocrine glands, vitamins, mineral salts (the electrolytes) and amino-acids.

(5) The evidence, slowly accumulating, points to nutritional deficiencies probably beginning during the period of gestation and due, in the main, to dietary errors and endocrine disturbances of the pregnant mother. The *prevention* of deafness, therefore, depends on the *mother getting an optimum diet* containing all the essential foods *during the gestation period*, and such dietary



habits must be carried on during babyhood, childhood and adolescence

(6) Finally, further work is necessary concerning the various factors referred to in this and other papers already published, and especially the nutritional, endocrine and allergic factors that may prove to be related to the enlargement of tonsils and adenoids.

### ***Surgical Treatment of Deafness—***

A wave of enthusiasm has swept the Country in favor of the surgical treatment of certain forms of deafness (otosclerosis). Lempert,<sup>12</sup> who must be credited with this renewed interest and perfected technic in what is in reality not a new thought, reports his results in 120 cases of *endaural fenestration of the external semicircular canal* with the following conclusions:

(1) No surgical risk to life is involved in fenestration of the external semicircular canal for the restoration of practical physiologic hearing to otosclerotic patients when this surgical procedure is performed under the strictest rules of asepsis.

(2) As a result of this surgical procedure, practical physiologic hearing has been permanently restored in about 80 per cent of properly selected cases of otosclerosis. The success of this work, of course, will always vary with the skill and patience of the operator.

(3) This operation should not be regarded as just another operative technic added to the list of operative procedures on the temporal bone. This operation blasts a trail for a new and different type of surgical treatment of the temporal bone. It is based on different surgical principles from any operation heretofore employed for the relief of suppurative lesions in this bone. The best results from this surgical procedure will be obtained by otologists who, in addition to extensive experience in all surgery of

the temporal bone, are possessed of a thorough knowledge and understanding of the principles of reconstructive plastic surgery.

(4) In fairness to the already successful development of surgical treatment of otosclerosis and for the protection of its still brighter future, no otologist, no matter how skillful a surgeon he may be, should attempt this particular operation without receiving special training in this type of procedure under supervision and guidance.

Campbell<sup>13</sup> discusses the factors necessary for obtaining favorable results in this operation such as, proper selection of cases, proper operative technic and post-operative care. In selecting cases, the following points must be observed:

1. Degree of deafness must be not greater than 60 to 65 per cent.
2. Bone conduction must be good.
3. Vestibular function needs to be adequate.
4. A fairly normal canal wall, tympanic membrane and middle ear.

Strict asepsis is essential in the post-operative care. Campbell feels that if it can be shown that these cases have gained a practical improvement of hearing or a reduction of the tinnitus and have retained the fistula beyond the time that bone regeneration should have occurred, then the operation can be considered as demonstrating the possibility of permanently improving the hearing. As the standards for selection of the patient become understood and the operative technic is developed and improved, it seems reasonable to assume that a high percentage of patients will obtain improvement of hearing by such surgical procedures.

Hughson<sup>14</sup> summarizes his experiences with the *round window graft operation* for deafness. In a series of 35 carefully controlled cases infection has

never occurred as a result of the approach to the round window niche through the wide incision of the tympanic membrane. The round window has not been ruptured, as evidenced by complete absence of any postoperative vestibular symptoms. During the period of direct observation possibly only with magnified binocular vision and brilliant illumination, the graft has never failed to remain fixed in the round window niche. This represents an interval well beyond the time when normal tissue grafts might fail to take and they had sloughed from their newly applied position.

Improvement in hearing, fulfilling standards previously enumerated, has been obtained following round window graft operations. The series has been small but has extended over a considerable period of time,  $3\frac{1}{2}$  years. When cases are selected according to the criteria listed above and when the surgical procedure is carried out as described, the operation is devoid of any serious immediate risk and in no instance has there been any late complication. Limitation of applicability apparently lies only in the age group above 50 years and to hearing losses greater than 50 decibels in the speech frequency range. It is hoped that the scope of the operation may be extended to the second decade age group after the hearing loss has reached a relatively static level.

*Postauricular approach* in operative treatment is described by Goodyear.<sup>15</sup> The author describes a method of postauricular approach with little or no disturbance of the middle ear, which is reasonably simple to perform, giving an excellent opening in the horizontal semicircular canal by means of an instrument which gives greater ease of control than a gauge or a chisel or electric burr. The author covers the fistula with the

thinnest layer of the meatal portion of the tympanomeatal membrane. In this method the middle ear is completely sealed off. This method was used in 2 cases.

Not all otologists are in complete agreement on the basic soundness of the operative treatment of progressive deafness. They are in accord with the self-evident immediate improvement, but when reliably compared to the knowledge of the pathology, only time will tell whether or not the operation can keep step with progressive degenerative changes. L. K. and P. Guggenheim<sup>16</sup> first of all state that the enthusiasm for this new operation is unwarranted. The authors failed to substantiate Canfield's conclusion that the use of the burnishing burr is not followed by new bone formation. The most favorable result as to fistula patency was achieved with a sharp chisel. The fistulas here reported were, as in Canfield's experiments, not in the labyrinthine capsule but in the membrane bone of the skull. The fact that the labyrinthine capsule consists of both membrane and cartilage has in no way affected the experiment, as all new bone formation, whether in the labyrinthine capsule or elsewhere, is by membrane-bone process. The otogenetic phenomenon of the transformation of cartilage model into bone model is strictly an otogenetic occurrence and never a repair process. In the final analysis of osteogenesis in artificial fistulas, the individual characteristics of primary germinal tissue (mesenchyme) will doubtless prove to be the determining factor just as they are in such conditions on chondrodystrophy and osteogenesis imperfecta and in connection with individual potentialities for future healing. The authors prefer the posterior approach.

**Aviation Deafness**—Airplane travel as a civil means of transportation has

taken a pre-eminent place, but now military necessities are focusing greater interest in the problem of aviation in relation to the ear. Campbell and Hargreaves<sup>17</sup> class the deafness of aviators according to the cause:

1. Acute fatigue of the end-organs of hearing and related structures.
2. Chronic accumulative fatigue of the end-organ and related structures.
3. Changes in middle ear pressure inherent with changes in altitude if ventilation of middle ear is faulty.
4. Chronic conduction deafness due to alternation in tissue resulting from faulty ventilation of middle ear.

The first 2 classifications are manifest by a decrease in acuity of hearing in the neighborhood of the 4096 area—a perception deafness. The last 2 classifications are manifest by a decrease in acuity for the lower frequencies (128-1024), a form of conduction deafness. The conduction deafness and perception deafness may be mixed to give any form of audiogram. The audiogram may be altered by the usual changes and hazards coincident with life.

Fatigue of the end-organ of hearing is due to noise and the effect of other vibratory energies inherent with flight. The 4096 area is peculiarly vulnerable because of its exposed position and possibly altered blood supply. Altitudinal decrease in oxygen may be a factor in the production of fatigue.

Physiologic or pathologic failure of the middle ear to be ventilated properly during altitudinal changes in pressure leads to acute or chronic changes in the middle ear, with the usual picture of conduction deafness.

Rapid advance in aircraft design and in flight regulation will decrease the problem of loss of hearing in those who fly in the future.

## Speech and Hearing

According to MacFarlan,<sup>18</sup> the testing of speech hearing must be approached with an understanding of the characteristics of speech. The patient is primarily interested in speech hearing. There is no correlation between speech hearing and frequency hearing. Speech hearing can be tested only by use of speech as a testing stimulus. The phonograph should be used in place of the old test with the spoken voice. A knowledge of testing for speech hearing and proper equipment should be used in the armamentarium of every otologist.

Perfect speech is dependent on perfect hearing, correct voice production, understanding of pitch, volume, and rhythm control and careful articulation, according to Goldstein.<sup>19</sup> Since speech is but an imitation of sound of the human voice as heard, defective speech often is the result of imperfect hearing. A lack of physical appreciation of pitch, volume, and rhythm due to defective hearing may contract all favorable elements in production of perfect speech.

In young children both dyslalia ("baby-talk") and word deafness are thoroughly amenable to correction in the hands of expert voice correctionists. The congenitally deaf subject can be taught the mechanics of rhythm, pitch, accent, volume, and quality of speech by application of sight and touch as a substitute for lost sense of hearing. School surveys reveal that 3,000,000 public school children in the United States have imperfect hearing and 4,000,000 demonstrate some defects of speech. This problem is distinctly the province of laryngologists who should clarify the attitude of parents, to emphasize proper surgical treatment in individual cases, and to create a better understanding of principles of preventative medicine.

Defects in speech in relation to defects in hearing are discussed by Voorhees.<sup>20</sup> Speech defects are even commoner than defects in hearing. Although defects of speech and hearing are closely allied at times, they are often separate and independent. The profoundly deafened person, however, always has trouble with voice production because he does not know whether he is speaking too loudly or too softly, distinctly or indistinctly.

Speech difficulties can be classified roughly under 5 headings, *i. e.*, (1) anatomic defects; (2) severe colds of childhood; (3) speech defects associated with loss of hearing for certain frequencies; (4) profound deafness in children is either congenital or acquired, and for the greater number it is acquired; (5) profound deafness in adults brings about changed quality of speech and *intensity*.

(The author stresses the importance of modulation *pitch*, and *intensity* of speakers, etc. This phase of speech training often is neglected. This defect of speech is common in the hard of hearing, especially nerve deafness. The importance of this is shown in those with defective hearing, who are not aware of this defect, in relation to their pitch.)

Medical phonetics as an essential part of otorhinolaryngology is discussed by Moses.<sup>21</sup> The more exact methods of modern experimental phonetics, which before have been used only for linguistic purposes, will gradually find their way into the otologist's office. The movements of the larynx, of the palate, and of the lips, as well as any air vibrations of voice and speech, can be registered with the same exactness as the electrocardiogram records the auricular and ventricular activity of the heart. It must be admitted that a great number of nervous diseases mentioned do not, strictly speaking, belong to the field of the otolo-

gist. These diseases, however, reveal symptoms in the organ of his field which can be detected only by a thoroughly trained otologist. Parkinson's paralysis, *e. g.*, affects the voice and help can be obtained in establishing a diagnosis by recording the inaudible microscopic tremulous movements of the larynx. Specialists interested in constitutional problems will find that the human voice gives new evidence and furnishes new clues for certain constitutional types. To the different constitutional types (Sigaud, Kretschner) are correlated different variations of voice. Thus, phonetics is able to enhance the importance of otorhinolaryngology and may be considered its fruit-bearing branch.

### Diseases of the External Ear

**External Otitis**—Diffuse external otitis in 3 cases associated with secondary anemia is reported by Alexander.<sup>22</sup> The disease was persistent and defied treatment until an associated secondary anemia was discovered. When specific therapy (*liver extract*) was instituted, the local condition of the ear responded. The author offers the suggestion that possibly the more protracted and obstinate cases of external otitis may be due to a relatively mild secondary anemia.

**Otomycosis**—It is the belief of Dart<sup>23</sup> that otomycosis is much more frequent than textbooks would lead one to believe and is frequently overlooked in the treatment of external otitis. The author feels that the entity has not always been treated properly and that recent experimental work has furnished better means of therapy. He states that powdered silver picrate is ineffective and recommends *metacresyl acetate* (*cresatin*) and *thymol* for its excellent fungicidal value.

*Aspergillus niger* infections in 2 cases are described by Felderman,<sup>24</sup> who be-

lieves that the incidence of this fungus in the upper air passages is more frequent than the literature would indicate. The author found that *silver picrate ointment* was effective and has fungicidal properties.

**Tumors**—Four cases, namely of (1) squamous-cell carcinoma, (2) adenocarcinoma, (3) fibrosarcoma, and (4) neurofibroma involving the middle ear, are presented by Rosenwasser.<sup>25</sup> The futility of any form of treatment of adenoid malignant growths is demonstrated by case I, in which the tumor, a squamous-cell carcinoma, had already extended into the substance of temporal lobes and by case II, in which the tumor, an adenocarcinoma, had extensively invaded the temperomandibular joint and zygoma.

As a general rule, all growths situated deep in the external auditory canal should be regarded as potentially malignant, regardless of whether they are associated with bloody discharge, pain or paralysis of facial nerve. Results of 1 biopsy, if negative, do not negate the possibility of malignant growth. In a patient with known chronic suppuration of the middle ear associated with polyps, a superimposed malignant growth may develop at any period of the infection. The onset of pain, paralysis of the facial nerve, or bloody discharge in chronic suppuration of the middle ear should cause suspicion of a neoplasm.

As to *treatment*, at present it is the consensus that *radical electrosurgical removal* combined with *intensive external irradiation* is the method of choice in the therapy of neoplasms involving the middle ear.

Eleven cases of tumors of the external auditory canal are reviewed by Mitchell.<sup>26</sup> Malignant tumors were found in only 3 cases, 1 cylindromatous lymphangioma, 1 keloid, 1 benign ulcer, and 5 osteomas, 3 of the latter having been operated. The

case histories of the patients reported are briefly presented and the recent literature on tumors of the external auditory canal is reviewed.

**Sarcoidosis**—A rather infrequent dermatological condition, commonly known as "*sarcoid of Boeck*," is presented in the form of a case report by Poe.<sup>27</sup> It was in 1899 that Boeck described nontender, noncaseating nodules as sarcoids because they resembled the small round-cell sarcoma histologically. Actually the picture is that of a noncaseating tuberculosis. The patient described by Poe was a 38-year-old colored woman who presented herself with hoarseness and shooting pains to the left ear.

### Acute Otitis Media

**Bacteriology**—Bacteriological studies of acute infections of the middle ear were conducted by Henry and Kuhn.<sup>28</sup> It seems significant that 116 cultures (23.7 per cent) showed no growth even though clinically these patients had an acute otitis media. Page reported that cultures from 23 per cent of his cases showed no growth and he seemed to regard it as "probably being in a faulty technique." The authors cannot agree with this viewpoint, for they feel there must be some other factors, otherwise why should these ears clear as soon as the pressure is released by myringotomy, even without much drainage through the external canal. In 6 of their cases there was enough pressure to produce spontaneous rupture of the membrane. The character of the discharge in these cases was usually mucoid instead of purulent in character.

The gram-positive cocci accounted for the greatest percentage of the infections in this series (95.6 per cent). Of this group, however, the staphylococcus was found in 32 per cent of the cultures. If these are added to those which showed

no growth it gives a total of 229 cultures or 47 per cent. **Sulfanilamide** and **sulfapyridine** are used extensively today in chemotherapy of certain types of infections. Many are giving these drugs empirically, and yet the authors know they are not without toxic effects on the patient, sometimes seriously. In this series there are 47 per cent of the cases that would have received little or no benefit from these drugs had they been used without first determining the type of infection, and damage might have been done. There were 37 per cent *Streptococcus hemolyticus* and 12 per cent *pneumococcus*, or a total of 49 per cent of these cases that we could expect benefit from the use of these drugs. There were 31 patients (6.6 per cent) that developed mastoiditis and were operated upon. Of the 31 patients, 19 had had myringotomies and 12 a spontaneous rupture, but if the number of myringotomy cases is considered, this is only 5 per cent of that group of cases, while 12 per cent of those that ruptured developed mastoiditis or  $2\frac{1}{2}$  times as many. Page reported 3 times as many cases of mastoiditis among those which ruptured spontaneously as compared to those in which myringotomy was done.

In their series they did not find the large number of pneumococcus Type III infections that are reported by Hacyopoulos and among the pneumococcal infections encountered there were no fatal cases. The duration of illness was in some cases considerably longer.

A case complicated by mastoiditis, meningitis and septicemia was recorded by Neter and Chait.<sup>29</sup> *B. proteus vulgaris* was isolated in cultures of material from all the lesions involved. The pathogenicity for man of the members of the genus *Proteus*, particularly in regard to meningitis and septicemia, is discussed. **Sulfanilamide** was not successful in the

cure but did result in freeing the blood of this organism (the concentration in the blood of the drug ranged between 1 and 2 mg. per 100 cc.).

**Treatment—Chemotherapy** — The recent literature still abounds in contributions to the rôle of **sulfanilamide** and its derivatives in the treatment of acute otitis media (Galloway<sup>30</sup>). As a result of an experience in 793 cases observed by Bowers<sup>31</sup> and an analysis of his experience in the previous 7 years, the author concludes that if chemotherapy is given early, before bone destruction occurs, the duration of the discharge and the number of mastoidectomies is diminished by about 50 per cent. He believes, however, that when the clinical picture suggests mastoidectomy, it is far safer to operate and that after an uncomplicated mastoid operation it is better not to give the drug. In *complicated mastoidectomy* Bowers believes the drug should be administered in intensive doses. Due to a well-known masking effect and possible toxic effects, it is at times necessary to stop the administration of the drug in order to obtain a true picture of the actual condition which exists. Some clinicians believe that the effect of the drug in acute otitis media has been overrated. Babcock<sup>32</sup> finds its greatest field of usefulness in *otitic meningitis*, where the mortality has been reduced from 96.8 per cent to 35 per cent.

**Sulfanilamide** in treatment of acute infection of the ear and of the mastoid in infants and in children is discussed by Hebble,<sup>33</sup> who reviews 17 cases of purulent infection of the middle ear indicative of involvement of mastoid so treated. On the basis of complete subsidence of the otorrhea within a reasonable period of time being considered as a standard for conservative cure, only 4 of the 17 patients treated with sulfanilamide responded favorably, and the remaining

13 came to operation. Certain conclusions regarding the amount of the dose of the drug, the period of administration, the alteration of certain clinical pictures and the feasibility of operation are drawn, based on the results and observations in the present study.

A follow-up of these 17 patients in the outpatient clinic has shown no recurrence of the infection of the ear or of the mastoid. The following conclusions as to administration of the drug are drawn: (1) These patients show a generally poor response to conservative medical treatment, including the use of sulfanilamide. (2) If the administration of the drug is not to be discontinued until there is a complete clinical cure, as recently advocated by Long and Bliss, it will require longer than 10 days to 2 weeks in many patients with this type of infection. (3) In view of the clinical observations and the relatively nontoxic effects of the drug as used in these cases, a larger dose and a longer period of use now seem not only safe to try but necessary for better results. (4) In cases of this sort in the wards of the otolaryngologic department of the children's hospital, if the patient's ear has been discharging less than 4 weeks, continuous sulfanilamide therapy throughout several weeks seems feasible, provided there are no definite toxic effects. (5) If the duration of otorrhea, however, has already exceeded 4 weeks when the patient is first seen, operation still seems advisable if the otorrhea and leukocytosis have shown no definite response after 10 days to 2 weeks of sulfanilamide treatment. After operation the drug may be administered to better advantage. (6) In the presence of intracranial complications, sulfanilamide does mask certain typical symptoms. This is to be kept in mind, but not to be offered

as a contraindication to the use of the drug.

Imhoff<sup>34</sup> administered sulfanilamide to 8 children suffering from *acute suppurative otitis media complicated by unilateral or bilateral mastoiditis*. The patients were about to be operated on because treatment with vaccines, stock vaccines, proteins and shock methods had failed and the x-ray examinations indicated the existence of a mastoiditis. Neither the dose nor the duration of the treatment is specified. The earache and the pain over the mastoid, the headache and fever diminished early in the course of the treatment and disappeared in from 10 to 20 days. Discharge from the ear diminished early and stopped altogether in from 20 to 30 days. Otoscopic examination performed before and after administration of sulfanilamide demonstrated the disappearance of the local edema, congestion and infiltration of the tympanic membrane and healing of the perforation of the membrane. Normal hearing returned in all of the cases. The author believes that this treatment is indicated in acute cases in which operation is indicated but not in the presence of fulminant general and local symptoms which call for an emergency operation.

Horan and French<sup>35</sup> review 621 cases of *suppurative otitis media* treated with *sulfanilamide*. The patients were given an emulsion of sulfanilamide by mouth in full doses according to age and weight. Medication was continued to a total dose of 10 drams (40 Gm.). Often the ear recovered before the maximal dose had been reached. Parenteral administration of *azosulfamide* was resorted to when it was thought advisable to reach the maximal concentration in the minimal time. *Sulfapyridine* was substituted for sulfanilamide if pneumococci were isolated. Many pa-

tients were treated as outpatients under constant supervision. No serious toxic manifestations were seen. The incidence of mastoiditis was only 3.4 per cent, compared with 22.7 per cent before the introduction of sulfanilamide therapy. The authors urge that all patients with acute suppurative otitis media be given sulfanilamide or sulfa-pyridine, because this will greatly reduce the incidence of mastoiditis and will allow a more conservative attitude to be adopted once mastoiditis develops.

**Convalescent Scarlet Fever Serum**—Viole<sup>36</sup> used human convalescent scarlet fever serum for 37 patients with streptococcic infection of the ear, nose or throat. Some of these were complications of scarlet fever or scarlatina. Of 16 patients having otitis media and mastoiditis, 9 required *mastoidectomies*. In 4 cases in which the *serum* was administered there was an immediate drop in temperature and lessening of the toxic symptoms, with rapid, uneventful recovery. In 7 the convalescence was slower but far better than might have been expected had the serum not been administered. The results were debatable in only 4 instances, as no demonstrable changes could be attributed to the serum. Only 1 of these 16 patients died in spite of an injection of scarlet fever serum, which seemed to have no effect. Necropsy revealed that death was due to an acute streptococcic septicemia. Eight of the 37 patients received *sulfanilamide* in addition to the *serum*. It made little if any difference in the course of the disease and the patient's recovery. In the presence, however, of a grave illness, neither should be denied if indicated. There were 5 cases of *streptococcic meningitis secondary to mastoiditis* in which *surgical intervention* was performed. Two of these patients im-

proved immediately after receiving the *serum*, although 1 had been receiving sulfanilamide without much effect. Convalescence was uneventful and the results were excellent. A third patient showed some immediate improvement but a large *abscess* developed in the left buttock at the site of the intramuscular injection of the serum. Progress was retarded until the *abscess* was *opened and drained*. The 2 remaining patients of this group received *sulfanilamide* in addition to *serum*. One made an uneventful recovery; the other improved slowly, but 4 days after discharge from the hospital a diagnosis of scarlet fever was made. The value of the serum may be considered questionable. Another patient immediately after *mastoidectomy* on the left side with ligation of the jugular vein received 40 cc. of *scarlet fever serum* and his temperature dropped to normal, where it remained for 4 days, when it rose suddenly to 105° F. (40.5° C.). The mastoid wound was reopened but no pathologic change was found. Two subsequent injections of serum, 20 and 40 cc. respectively, failed to elicit any response and the patient died. There were 4 cases of *laryngotracheobronchitis* and 3 of *streptococcic pharyngitis*. Three *tracheotomies* were performed. The rate of recovery and definite signs of improvement were much slower in 3 patients who were given sulfanilamide in addition to the serum. The others who received only *serum*, except 1 on whom a tracheotomy had been performed, improved immediately.

The author states that the most dramatic improvement following serum occurred among 5 cases of *streptococcic sore-throat*, definitely placing streptococcic sore-throat among the curable diseases. In the series there was a *retropharyngeal abscess* with complicating



cervical adenitis, toxic anemia, Ludwig's angina and otitis media. In spite of injections of *serum*, this patient's progress was slow until the *abscess* was *opened and drained*, when the convalescence was rapid and uneventful. This emphasizes the benefits of early treatment. One instance of beginning *peritonsillar abscess* responded well to *scarlet fever serum* and the patient improved without surgical intervention. On the other hand, its value in a case of *cervical adenitis* was questionable. The patient also received *sulfanilamide* and, though her convalescence was uneventful, it was decidedly slow. There was only 1 reaction to the serum. This patient had a long history of allergy to adenitis and pneumonia complicating scarlet fever. Urticaria developed after 40 cc. of the scarlet fever serum, and no more was given. After adequate doses of sulfanilamide she recovered. Human convalescent scarlet fever serum produces no foreign protein reactions and sensitizations as does animal serum, and such reactions as may occur are easily controlled.

### Mastoid

**Atypical Mastoiditis**—Singleton<sup>37</sup> gives a report of cases of an adult type and offers the following conclusions:

1. Atypical mastoiditis, the so-called primary mastoiditis, occurs chiefly in adults.
2. It runs a mild course, with few local or general signs and symptoms of the disease.
3. The presence of edema in the superior-posterior bony canal wall and good x-ray pictures of the mastoid are the most reliable diagnostic aids.
4. Fatal complications are rare.

**Acute Mastoiditis Masked by Sulfanilamide**—Rosen<sup>38</sup> describes a case of an extensive mastoiditis with extradural abscess which was treated by sul-

fanilamide. The patient had fever, slight nystagmus, leukocytosis, but no discharge, no tenderness and good hearing. The symptoms being attributed to the sulfanilamide, the drug was stopped. Three days later there were pain, discharge and marked mastoid tenderness. Surgery was done.

**Mastoidectomy**—1. *Simple Mastoidectomy*—A critical analysis of 100 consecutive cases of simple mastoidectomy, with 1 death, is presented by Tomb<sup>39</sup>. Closure of the periosteum aided in the formation of new bone. The use of noncompression bandages resulted in less postoperative edema of the tissues. Mastoiditis was most frequent in those between 5 and 10 years of age. Many mothers of such children are believed to have been infected by them. The frequency of mastoiditis was greatest in February and March and least in August, September and October. Paracentesis was believed to be advisable. The optimum time for operation was believed to be about the third week of otitis media. Before that time there is little localization, while later vital visceral structures are more frequently attacked. In acute mastoiditis superimposed on chronic purulent otitis media, simple mastoidectomy with removal of all eburnated bone was found to be sufficient. In recurrent mastoiditis formation of new bone was not found in less than 1 year after the previous operation. A revision mastoidectomy was indicated when sepsis with threatening symptoms was present or when faulty healing had occurred.

Cultures of material from the mastoid yielded in 54 per cent of cases a *Streptococcus hemolyticus* and in 12 per cent a pneumococcus. Streptococcus infection was associated with fulminating symptoms and numerous complicating lesions, while pneumococcal infection

was practically symptomless, but caused extensive destruction of bone.

**2. Radical Mastoidectomy**—The effect of radical mastoidectomy upon hearing is analyzed by Maxwell and Richter.<sup>40</sup> Preoperative loss of hearing seems to be determined to a considerable degree relatively early in the chronic suppurative process. A relatively poor prognosis for renewed hearing after a radical mastoidectomy may have to be given to persons over 45 or 50, to those in whom infection of the middle ear and mastoid is of short duration and also perhaps to those who have comparatively good preoperative hearing as indicated by an average loss in the critical frequencies of less than 25 or 30 decibels.

In the consideration of radical mastoidectomy for a patient in whom the indications for the procedure are clear, the possibility of decreased residual hearing should not act as a deterrent. In the majority of cases the chances that the hearing may be slightly improved or slightly impaired are about equal. In either event the average change is less than 10 decibels.

**3. Care of Wounds**—In the care of mastoid wounds following mastoid operations some clinicians have been enthusiastic about such preparations as *sulfanilamide* or *sulfathiazole powder* and *sulfamerthiolate powder*. Lion<sup>41</sup> describes his method of hastening epithelization by the use of *scarlet red ointment* in the postoperative care of radical mastoid operative cavities. He uses a special syringe for this purpose.

### Otogenic Complications

**Encephalography**—The value of encephalography in the diagnosis of otogenic intracranial complications is emphasized by a case report of Dinolt.<sup>42</sup> In juvenile or adolescent patients suppurative otitis media, papilledema, head-

ache, vomiting, and increased pressure of the spinal fluid can be explained, as described by Symmonds and others, as a result of *otitis hydrocephalus* but also as a consequence of (1) *swelling of the brain*; (2) *edema of the brain*; (3) *serous meningitis*; (4) *nonsuppurative encephalitis*. Encephalographic examination should be used to help in distinguishing them. As a favorable prognosis results from this procedure, the ventricles can also be filled with air in cases of increased intracranial pressure without harm to the patient, if the necessary precautions are observed and the disease is localized within the middle fossa. A case is reported in which the encephalographic examination, if performed at the proper time, would have prevented surgical cerebral exploration but when performed later in the course of the disease, aided in making and confirming of the diagnosis and in the improvement of the patient's condition, which was most likely produced by an edema of the brain. The presence of a cervical rib complicated the clinical picture, producing peripheral brachial palsy. Complete recovery ensued. The use of the term "otitic hydrocephalus" should be restricted solely to that condition as proved by encephalographic examination. The prognosis, even with a higher degree of papilledema, is favorable even without much decompression of the brain, as proved in a second case, in which a 6 D. papilledema gave way to normal condition.

In the same connection, cerebral edema as the cause of intracranial hypertension of otitic origin, is presented by Levy<sup>43</sup>. A case of *otogenous intracranial hypertension* is described in which the pneumographic and operative findings indicated that the increased pressure was due to an excessive amount of fluid in the brain itself rather than, as is gener-

ally assumed, in the ventricles and subarachnoid spaces. Similar cases, with and without pain of suppuration in the temporal bone, have been described in the literature and have been variously termed serous meningitis, hypertensive meningeal hydrocephalus, probably incorrect in many cases, as the presence of dilated subarachnoid channels and a communicating hydrocephalus has not been demonstrated in most of the reported cases. The term "otitic hydrocephalus" is used in an extremely loose and vague fashion both in the otologic and neurologic literature, and often includes cases of obstructive non-communicating hydrocephalus due to arachnoidal adhesions, erupted subarachnoid collections of fluid and reactive meningitis, as well as cases of communicating hydrocephalus. It seems to the writer that careful efforts should be made to determine more accurately what type of intracranial disturbance is present. In those cases in which the hypertensive syndrome subsides after simple lumbar drainage, it seems best to apply simply the descriptive term "*hypertensive syndrome*" rather than such terms as "otitic hydrocephalus" or "hypertensive meningeal hydrops," for the reasons already mentioned. In cases which do not respond to lumbar drainage and dehydrating measures, pneumographic studies (preferably ventriculography) should be done. In such cases the nature of the pathology then will be disclosed at least partially and the proper therapeutic procedures can be carried out.

In the case under discussion, a persistent cerebral edema was found to be the cause of the intracranial hypertension and the suggestion is offered that venous stasis due to infection in the dural sinuses might be the underlying etiology. It is also suggested that cerebral edema might be a much more frequent cause

of the otogenous hypertensive syndrome than is generally supposed.

**Meningitis — Treatment** — In a series of 15 consecutive cases of meningitis, reported by Cuning,<sup>44</sup> 11 patients recovered and 4 died, giving a mortality of 27 per cent. Sulfanilamide, while obviously extremely important, is apparently not sufficient in itself to produce a cure. Surgical intervention in itself is not sufficient and it seems that a combination, *i. e.*, **sulfanilamide and surgical intervention** offers the best hope. In the use of the drug, it is important that treatment be started early, that the dose be large, and that the treatment be continued for several weeks after cessation of symptoms. Surgical measures likewise should be instituted as soon as the diagnosis is made. In 7 of 8 cases in which the invading organism was *Streptococcus hemolyticus* the patient recovered. In 2 cases in which the organism was pneumococcus type I, and 1 case in which the organism was pneumococcus type III, the patient died. Had sulfapyridine been known when the pneumococci infections were treated, the results might have been better. Six patients showed paralysis of the external rectus muscle. While the author realizes that this is not a large series of cases, it seems, nevertheless, that with the use of sulfanilamide plus surgical intervention, meningitis is not necessarily to be considered so formidable as heretofore.

The description of a patient with a pneumococcus type III meningitis and recovery following the use of sulfapyridine is recorded by Ersner, Myers and Hayes.<sup>45</sup> This case illustrates that, despite the apparent efficacy of the **sulfapyridine** against the pneumococcus, at times the drug alone may be insufficient to overcome the infection. The addition of the **specific sera** to the treatment enhances its therapeutic value. In this par-

ticular case the concentration of the sulfapyridine in the blood closely followed the dosage. The boy received large dosage of sulfapyridine over a long period without ill effect. The dose of the sulfapyridine should be regulated by the condition of the patient and the concentration in the blood rather than by a table of dosage. The complete eradication of the fixed focus of infection in the mastoid and in the apical carotid portion of the temporal bone is always an important part of the treatment of meningeal complications of otitic origin.

Recently there has been some comment about the effectiveness of **sulfathiazole** in the management of *Staphylococcus aureus meningitis*. It has always been known that the mortality rate of this type of meningitis, especially in childhood, is high. While recovery has occasionally occurred by various methods of treatment, it seems, from recent experiences that sulfathiazole offers more reliable hope in what may otherwise be fatal cases. Theoretically, the new drug should be effective. It has, however, not been widely employed in *Staphylococcus aureus meningitis* to make a positive statement possible. Dietel and Kaiser<sup>46</sup> report a cure in a child 20 months old in whom a positive bacteriology of the meningitis was established. **Sulfathiazole** was administered by mouth through a stomach tube; 40 grains (2.6 Gm.) a day was given for 9 days. Daily **spinal punctures** were performed with **saline irrigations**. Gradually the child improved, with a clearing of the spinal fluid and disappearance of the bacteria. At the end of 3 weeks there was complete recovery. Numerous **blood transfusions** were given but no other drug was used. The sulfathiazole concentration of the blood never reached more than 3.5 mg. per 100 cc. of blood.

Against this claim of success is a warning by the manufacturers that sulfathiazole should not be used in the treatment of any type of meningitis because the drug does not pass over readily into the spinal fluid. "It would seem best, in light of present knowledge, to proceed cautiously in administration of this drug to patients who have previously suffered a toxic reaction in the course of therapy with sulfanilamide or sulfapyridine." Side-effects have occurred as have certain unpleasant reactions, but these have been of a transitory nature when the drug is discontinued at the first suggestion of untoward effects.

In the light of this information, the report of Dietel and Kaiser is of special interest, but further clinical experience is necessary before a more general utilization of the drug in meningitis can be fearlessly recommended.

**Sinus Phlebitis**—Recent literature contains additional reports of unusual cases and features in the successful rôle of **chemotherapy in conjunction with surgery**. In a chronic suppuration with an acute exacerbation, Hubert<sup>47</sup> reports recovery of his patient whose sepsis failed to respond despite obliteration of the lateral sinus and ligation of the internal jugular vein, until he administered **sulfanilamide**.

Brownell<sup>48</sup> describes 8 unusual cases of **thrombosis of the sigmoid sinus**. Thrombosis may be entirely asymptomatic and found only accidentally at mastoidectomy. The thrombosis may seal itself off at both ends, precluding embolic phenomenon, and drain itself by destroying the parietal wall of the sigmoid sinus; cholesteatoma may be found in the lumen of the lateral sinus. Meningitis, abscess of the brain, and thrombosis of the sigmoid sinus apparently produces localizing signs of abscess of temporo-sphenoid lobe.

In a panel discussion led by Dean,<sup>49</sup> the following high lights were brought out: Use of large doses of *sulfanilamide*, *sulfapyridine*, or *sulfathiazole* immediately, either by mouth or parenterally (3 grains—0.2 Gm. per kilogram body weight—give half of this as first dose). The x-ray film is slightly more transparent with use of this drug. Use of sulfanilamide powder fails in improving the record of the other powders now used. The ear becomes dry sooner, but is more hypersensitive and bleeds more. Also, these drugs (as a 1 per cent solution) are used in irrigating infected wounds or at least in keeping them clean. However, the drugs have *washing* effects. Furthermore, the symptoms of use of drugs may simulate those of intracranial complications. There is no definite clinical evidence that the drugs influence infectious processes in bones. Every case of acute otitis that has been subjected to chemotherapy should be very carefully watched after discontinuance of the therapy.

There seems to be no evidence that thrombosis or ligation of 1 lateral sinus produces or increases papilledema. The x-rays cannot be depended upon to diagnose sinus thrombosis. Anatomic anomalies of the lateral sinus are rare (its position, however, may vary).

**Transfusions of blood** in the care of patients after operations for otitic sepsis are described by Sutherland.<sup>50</sup> From a comparative study of the data presented and an examination of the photomicrographs showing the characteristic changes in blood and bone-marrow which take place during the course of otitic sepsis and the fatal renal hemorrhages resulting from the transfusion of incompatible blood, the following conclusions may be formulated: To influence or control effectively the activities of the individual types of cells in blood and tissues,

specific information must be acquired concerning their fundamental physiology and relations, not only to each other, but to the other cells and functions of the body. The effectiveness of preoperative or postoperative transfusions of blood in alleviating or controlling the adverse activities of blood, bone-marrow and parenchymal organs in otitic sepsis is not dependent on the choice of the direct or indirect method of intravenous injection. Their efficiency depends on their fulfilling the purpose for which they may be given: to replace erythrocytes lost in anemia; to restore the level of plasma protein, hemoglobin and oxygen carriers; to counteract leukopenia (in rare cases) and to increase the blood volume and water balance, thereby diluting toxic blood.

The use of *immunotransfusion* is different in purpose, in that its therapeutic value depends on the antibodies and other immune substances contained in the donor's blood, rather than on the blood elements themselves. Type specificity of various strains of organisms encountered in otitic sepsis complicates the question of immunity. This is particularly evidenced in efforts to compile clinical data correlated with bacteriologic investigations of the biologic behavior and antigenic structure of the troublesome triumvirate, streptococcus group A, and may culminate, in the near future, in the establishment at convenient centers of a co-operative service of direct specific biologic therapy.

Irrespective of the type of blood to be transfused or method of its administration, the transfusion of blood should not be considered a casual routine procedure. With definite indications for its use, the value of blood therapy for otitic sepsis may be greatly enhanced by administering it at the earliest indication that it is needed and by repeating it as

often as it is required while the recipients' defense forces are capable of responding and before sepsis or toxemia or both are overwhelming.

**Brain Abscess**—The significance of *aphasia* as a symptom of *otogenic extradural* abscess is discussed by Altmann.<sup>51</sup> As a symptom of an otogenic extradural abscess of the middle fossa, *aphasia* is rare. The report of 2 cases and a review of the literature show that *aphasia* in some instances of extensive abscesses may be caused merely or mainly by external pressure exerted by the abscess; in the majority of cases inflammatory involvement of the leptomeninges and of the superficial layers of the brain with collateral edema in the neighborhood may be the main factor in the development of *aphasia*. Because of the similar development mechanism of *aphasia* in these cases and in cases of abscess of the temporal lobe, a differential diagnosis of the conditions is always difficult. Only in cases in which there is a predominance of external pressure can the diagnosis be established with a degree of certainty, whereas in cases in which the inflammatory changes are predominant, the differential diagnosis becomes practically impossible.

**Facial Paralysis**—The *etiology* and *treatment* of seventh nerve paralysis is presented by McCaskey.<sup>52</sup> The etiology is classified as (1) trauma, (2) infection, (3) exposure, (4) neoplasm, (5) general systemic disease, (6) toxic and allergic. These lesions may be divided into 3 subdivisions (nucleogeniculate, geniculoforaminal and extraforaminal), as well as 2 main divisions of the facial nerve (supranuclear and infranuclear). The nonsurgical treatment consists of medical (drugs, allergins, etc.), physical therapy (heat, galvanism), and manipulative (massage and exercise). The surgical treatment consists of intracranial

surgery, plastic procedures on facial muscles, anastomosis of the seventh with other motor nerves, repair of the seventh nerve proper, and decompression of the nerve.

Hematoma of the facial nerve following simple *mastoidectomy* with decompression and gradual recovery of function was reported by Freedman.<sup>53</sup> The facial paralysis developed 24 hours after a simple mastoidectomy. Later, a radical mastoidectomy was done to attempt the restoration of facial nerve. Finally, upon a third operation, the active descending portion of the facial nerve was exposed from its canal. A blood clot within the nerve sheath was revived. Only during the seventh postoperative month has any improvement been noticed.

The management of facial paralysis by physical measures is discussed by Newman, Berris and Bohn.<sup>54</sup> They state that the treatment of facial paralysis is dependent on its various etiologic factors, on the question of whether the paralysis is of central or peripheral origin, and on the site of the lesion. They managed 30 cases by the use of physical therapeutic measures. The ages of the patients ranged between 6 and 79 years, average 37. With the onset of an acute refrigerans type of facial paralysis, *iodides* in saturated solution of *potassium* or *syrup of hydriotic acid* are indicated for their general alterative action. *Analgesics* are valuable. *Saline laxatives* are used during the acute stage of inflammation for their possible detergent effect. The physical measures applicable during the acute phase of the refrigerans palsies are directed toward the reduction of the inflammatory exudate and toward keeping the denervated muscles in position of physiologic rest. Decongestion at the stylomastoid foramen can be accomplished by *cantharides plasters*, *hot moist applications*, *ra-*

*diant heat, negative galvanism* and conventional or short-wave *diathermy*. The frequency of application is indicated by the pain and the tolerance of the tissues. To prevent muscles from stretching, they are supported by attaching 2 Y bands of *adhesive tape at the zygomatic bone and temporal region*. *Positive galvanism* is especially efficacious for the relief of *pain*. With the subsidence of the acute symptoms within 8 to 10 days, testing for reaction of degeneration is instituted. When no reaction of degeneration is present, recovery can be expected in from 2 to 8 weeks.

If a sufficient amount of recovery is not obtained after 6 months of rigorous physical therapeutic measures, surgery is to be considered. Active treatment now consists of *heat, massage, voluntary exercise* and *electrical stimulation* (with interrupted galvanic, sinusoidal and faradic currents). *Diathermy* or *radiant heat* is applied to the paralyzed side of the face for from 15 to 30 minutes. Another method of promoting a circulatory response consists of the common ion transfer of 0.5 per cent *acetylbetamethylcholine hydrochloride*. From 15 to 20 ma. of the *galvanic current* for 20 minutes is adequate. *Negative galvanism* for its heating effect can be applied for 30 minutes *over the stylomastoid foramen*. The strength of current should be just less than the amount required to cause a contraction of the muscles on the unaffected side. On the first day 3 contractions over the motor points are sufficient, and on subsequent days the number of contractions is increased but always kept within the fatigue range of the muscle. After 1 or 2 weeks the *slow sine wave* is substituted, from 20 to 30 contractions per minute being used. When the *faradic current* can be tolerated, it should replace the sine wave current. *Gentle*

*stroking massage* which follows stimulation preserves muscular tone. *Exercise of the facial muscles* is carried out *in front of a mirror* every day.

The *etiologic agent* must always be *removed* before physical measures are instituted. Seventeen of the 30 cases followed exposure, 6 middle ear disease, 1 dental manipulation, 1 trauma associated with an automobile accident, 2 head colds, 1 mumps, 1 an operation on the eighth nerve for vertigo, 1 a postpartum infection, and 2 mastoidectomy. In the 17 cases of exposure paralysis, a partial reaction of degeneration or no reaction of degeneration was present after 10 days.

### Head Injuries

In discussing disturbances of the function of the ear after concussion of the brain, Brunner<sup>55</sup> states that a symptom-complex can be observed which consists of headache, dizziness, inordinate fatigue on effort, intolerance to intoxicants, vasomotor instability, tinnitus, nausea, emotional instability, psychical depressions, psychical irritability and diminution of ability to remember and to concentrate. This symptom-complex has been variously described as postconcussion neurosis, postconcussion syndrome, traumatic encephalopathy, etc. It is associated with the following changes in the brain: Hemorrhages of the meninges leading to a thickening of the meninges and an obliteration of the meningeal spaces; dot-like hemorrhages in the medulla oblongata and in the cervical part of the spinal cord; foci of crushing and degenerations of fiber tracts. The pathological changes of the encephalogram after concussion include: Dilatation of ventricles; considerable accumulation of air on the convexity of the brain; migration of the ventricular system toward the site of the lesion; and

nonvisualization of the ventricular system after lumbar injections of air.

Postconcussion syndrome uncomplicated by injury to the temporal bone does not include marked cochlear symptoms. There is no definite impairment of hearing and tinnitus is neither frequent nor very bothersome. Labyrinthine symptoms, on the other hand, occur in 57 to 75 per cent of the cases. *Labyrinthine vertigo*, which is a sensation of whirling dizziness, must be distinguished from the vertigo which is described by the patient as giddiness, dizziness, swimming in the head, staggering or unsteadiness of motion. Labyrinthine vertigo is due to involvement of the labyrinth or the central pathways of the vestibular nerve; all other kinds of vertigo may have some correlation with the vestibular pathways, but it is not definitely known. Consequently, only the labyrinthine vertigo is considered an otological symptom. The presence of spontaneous nystagmus or of nystagmus induced by quick movements of the head confirm the existence of labyrinthine vertigo. The labyrinthine tests generally show either normal excitability or hyperexcitability of the labyrinths. If there is hypoexcitability of the labyrinths, the case is generally not a plain postconcussion syndrome but rather a complicated postconcussion syndrome, the complication being either a fracture of the temporal bone, a concussion of inner ear, a severe hemorrhage into the posterior fossa, a brain tumor, or another accompanying disease such as syphilis.

**Postconcussion Syndrome Complicated by Fractures of the Temporal Bone**—Fractures of the otitic capsule may involve the cochlea with an isolated loss of hearing and a retention of the function of the labyrinths. On the other hand, cases also have been reported proving the existence of an isolated fracture

of the vestibule but not of the cochlea. Hemorrhage from the ear following head injury is generally accepted as evidence of longitudinal fracture of the temporal bone. Drainage of cerebrospinal fluid from the ear may occur in transverse as well as longitudinal fractures. The prognosis in such cases is grave but is not as bad in the latter as in the former. After transverse fractures, there is in the great majority of cases a total deafness and a total loss of excitability of labyrinths. Longitudinal fractures cause a varying degree of hearing loss in over 50 per cent of the ears, the diminution of hearing being more often of an inner ear type than of a middle ear type.

Exact otoscopic examination in the acute stage of injury is unnecessary and may be dangerous. It should be done only if the patient complains of pain or if there is a purulent discharge from the ear.

**Postconcussion Syndrome Complicated by Concussion of the Inner Ear**—Concussion of the inner ear includes all changes of the internal ear following a head injury which did not fracture the bony capsule of the internal ear. These changes are probably brought about by the transmission to the labyrinthine fluids of the acute increase of intracranial pressure at the moment of injury, and by the disturbance of the blood circulation of the inner ear. Deafness is the chief symptom. It is generally unilateral and most frequently of the middle and inner ear type. The labyrinthine tests show either a normal excitability or a hypoexcitability of the labyrinths. Occasionally a loss of excitability for the caloric test is seen, while the turning test yields normal responses.

Deafness after a head injury may be due to (a) transverse fracture; (b)



longitudinal fractures; (*c*) isolated fracture of the cochlea; (*d*) concussion of the inner ear; and (*e*) to an exacerbation of an old ear disease by a psychic shock. The following symptoms might help in making a diagnosis. In transverse fractures there is an immediate total loss of hearing on 1 side, combined with a total loss of excitability of labyrinth on the same side, and the x-ray picture shows the fracture in the majority of cases. As far as the longitudinal fractures are concerned, the cases which are combined with a concussion of the inner ear must be distinguished from those cases which are not. In the first group there is a subtotal loss of hearing which frequently increases after the injury, and the excitability of the labyrinths is, as a rule, present as far as the turning test is concerned. In the second group there is, as a rule, a marked diminution of hearing immediately after the injury, which, however, improves later, and there is a normal excitability of the labyrinths. In both groups of cases the x-ray examination frequently shows the fracture. In isolated fractures of the cochlea there is a total loss of hearing on the injured side, the excitability of the labyrinths is normal or subnormal, and the x-ray examination, as a rule, shows the fracture. In concussion of the inner ear there are the same findings as mentioned above concerning the cases of longitudinal fracture with concussion of inner ear. The x-ray examination, however, does not show any fracture. In otosclerosis and arteriosclerosis of the inner ear the history is of importance, particularly when there was some deafness and tinnitus present prior to the accident. The deafness is most often bilateral, the labyrinthine excitability is

normal or supernormal, and the x-ray examination fails to show any fracture.

The material reviewed by Saethre<sup>56</sup> consists of 574 patients with 589 injuries: 258 were early and 316 late cases. The importance of alcoholism is demonstrated by the fact that in 30 per cent of the new cases the patient was under the influence of alcohol when brought into the hospital and that one-third of the patients with traumatic psychoses were chronic alcoholic addicts. The syndrome of *commotio cerebri* existed in 67.5 per cent of the head injuries. Loss of consciousness persisted in three-fourths of the cases for less than 2 hours. Of those in which loss of consciousness persisted for more than 24 hours, only 5 presented the pure syndrome of *commotio cerebri*. Neurologic disturbances were observed in 53.7 per cent of the new cases and in 35 per cent of the late cases. In more than half of the late cases otologic symptoms predominated. Olfactory paresthesias and anosmia were likewise relatively frequent. Traumatic epilepsy was observed in 5 per cent. The author regards it as inadvisable to apply the term "*traumatic neurosis*" to the subjective symptoms of patients with head injuries; he believes that this term should be restricted to cases in which intracranial lesions are absent. He suggests that the subjective symptoms be classified into (1) the traumatogenic cerebral general syndrome (headaches, vertigo and difficulties in thinking) and (2) psychogenic symptoms: (*a*) primary, those due to shock and (*b*) secondary, the psychoreactive and compensatory symptoms. The traumatogenic cerebral general syndrome predominated in 49.4 per cent of the cases, the psychogenic symptoms in 24.8 per cent, and the organic neurologic symptoms in 25.77 per cent.

## ENDOSCOPY

By LOUIS H. CLERF, M.D., LL.D.

**Anesthesia**—Peroral endoscopic procedures may be performed with a minimum of discomfort and a maximum of safety and objectives may be attained satisfactorily if there is adequate anesthesia. In outlining the technic of administering local anesthesia for these procedures, Putney<sup>57</sup> expressed a preference for *pontocaine hydrochloride*, 1 per cent, to be applied topically to the pyriform sinuses or used as a gargle, and for instillation of *larocaine hydrochloride*, 2 per cent, into the larynx and trachea. The importance of the time element, of the amount of solution employed, and of placing the medication in the desired locality was stressed. In anesthetizing the larynx it is desirable to fractionate the dose. Sedatives are valuable supplementary aids and should be used for all diagnostic bronchoscopic examinations and for removal of foreign bodies. Children tolerate large doses of *morphine* remarkably well.

**Bronchial Obstruction**

While *bronchoscopy* is of value in the diagnosis of bronchial obstruction, Gittins<sup>58</sup> emphasized its importance as a means of treatment in many of the pulmonary conditions which often are diagnosed erroneously as bronchopneumonia. Bronchopneumonia often is atelectasis secondary to mechanical obstruction of a bronchus by masses of mucus. This is observed more often in infants and young children who have greater difficulty in getting rid of thick bronchial secretions. Bronchoscopic aspiration of secretions not only relieves the overloaded cilia, but prevents serious bronchopulmonary changes resulting from long continued stagnation.

**Acute Laryngotracheobronchitis**

Difficulty in maintaining an adequate airway in cases of acute laryngotracheobronchitis even after tracheotomy, commonly results from obstruction of the trachea and bronchi with thick and inspissated secretion. One of the most important recent contributions in treatment, *i. e.*, the employment of means to humidify the inspired air, was described by Davison.<sup>59</sup> He employed a mechanical *humidifier* which is connected with the canopy of an oxygen tent. This is very efficient, for it recirculates and re-humidifies the air in the tent canopy. With this apparatus it is possible to build up quickly and to maintain a relative humidity of 95 per cent. Subglottic edema is less marked if the patient is kept in cool moist air rather than in warm moist air.

The employment of *sedatives and atropine* is *contraindicated*, since they tend to inhibit cough and dry up bronchial secretion. The development of pneumonia usually can be prevented if treatment is begun early and if bronchi are kept open at all times by removal of secretions and obstructing crusts. *Secretions* are readily removed by *aspiration* through the tracheal cannula, and *bronchoscopy*, if indicated, may be performed through the tracheal fistula. Instillation of a *solution of sodium bicarbonate* or *sodium chloride through the tracheotomy tube* has been advocated to soften tracheal crusts. The use of *humidified air* has rendered this practically unnecessary. He expressed the opinion that *sulfanilamide* is of value when *Streptococcus hemolyticus* is the infecting organism.

In cases of acute laryngotracheobronchitis due to a staphylococcus, Evans<sup>60</sup>

employed a *bacteriophage* which was instilled into the trachea at frequent intervals through the tracheotomy tube and soon removed by suction. After each instillation of phage solution there was induced a paroxysm of coughing and evacuation of quantities of thick, viscid, purulent secretion. He considered as important essentials in the treatment of these patients, constant and competent *special nursing, humidification of the air*, maintenance of an adequate airway by *tracheotomy*, frequent *aspiration of secretion* through the cannula and bronchoscopic *removal of crusts* when indicated.

In addition to employing the commonly accepted methods of treatment for relief of dyspnea and removal of secretions and crusts from the trachea and bronchi in cases of acute laryngotracheobronchitis, Galloway<sup>61</sup> has found *postural drainage* a valuable adjunct. With the head and shoulders of the patient lowered, he has found that secretions and crusts are gotten rid of more readily by suction after instillation of a *warm sodium bicarbonate* or *epinephrine solution* into the trachea through the tracheotomy fistula.

### Allergy

*Acute laryngeal obstruction* may be allergic in origin. In 2 cases of acute obstruction reported by Chang<sup>62</sup> there was specific sensitivity to milk. In 1 case the allergic manifestations involved the larynx and gastrointestinal tract. In another tracheobronchial tree as well as larynx was involved. In both cases *tracheotomy* became necessary for relief of dyspnea. Appropriate treatment was instituted as soon as the cause was discovered. These cases emphasize the importance of considering allergy as an etiological factor in the management of patients with laryngeal obstruction.

In a study of *obstructive atelectasis* in allergic children, Friedman and Molony<sup>63</sup> discussed the etiologic factors and means of treatment. Treatment should first be concerned with giving relief to the patient and secondarily with the prevention of recurrences. If the atelectasis persists in spite of the usual employment of *postural drainage, expectorants* and *epinephrine hydrochloride, bronchoscopic aspiration of the thick tenacious bronchial secretion* is the method of choice. Repeated aspirations of the air passages may be necessary before adequate ventilation of the bronchi is secured.

In a bronchoscopic study of 140 patients suffering from *asthma*, Prickman and Moersch<sup>64</sup> found definite stenosis of 1 or more bronchi in 60 cases. The more prominent symptoms noted were severe, persistent, at times paroxysmal cough and fever. The persistent coughing apparently is caused by the patient's attempt to raise secretions retained beyond the point of stenosis. The febrile reaction probably is due to retention of secretion, for fever commonly subsided as the expectorated secretions increased in quantity.

*Treatment* in these cases consists of *dilatation of the stenosis* by means of forceps introduced through the bronchoscope and *aspiration of secretions*. Subsidence of fever, reduction of the quantity and change in character of the sputum, improvement in the course of the asthma, and often prompt clearing of the physical signs of bronchial obstruction occur. *Recurrences* are noted but usually can be *prevented by avoidance of respiratory infection and postural drainage*.

### Postoperative Pulmonary Atelectasis

The prevention and treatment of postoperative atelectasis are of great concern

to all anesthetists. Although many theories have been advanced concerning the cause, Mousel<sup>65</sup> expressed the opinion that in most instances it results from mechanical obstruction. This may be due to plugging of 1 or more bronchi by tenacious secretions which have collected in the tracheobronchial tree during anesthesia, or which was present preoperatively and by mucus, blood or vomitus which have been aspirated into the trachea either during or immediately following anesthesia.

If there is any question of inspiration of material into the trachea during anesthesia, bronchoscopic aspiration should be resorted to before the patient leaves the operating table. This can be done without difficulty before the patient has recovered from the anesthetic. Post-operative atelectasis can be treated successfully by *bronchoscopic aspiration* in a majority of instances. It is important that this is resorted to promptly in order to prevent pneumonitis or pulmonary supuration.

### Pulmonary Abscess

While there is no unanimity of opinion as to the best method of treatment of pulmonary abscess, it also is obvious that no single method can be applicable to all cases.

Arbuckle<sup>66</sup> expressed the opinion that the duration of the abscess and the severity of the infection may be diminished by proper *bronchoscopic drainage*. By bronchoscopic treatment is meant destruction of granulation tissue by the employment of forceps and curettes, removal of the contents of the abscess by means of special aspirating tubes made for this purpose that are introduced directly into the cavity and the instillation of *guaiacol* with 1 per cent *oil of sweet almonds* or *iodized oil*.

In an experience of 43 consecutive cases which included cases of acute, sub-acute and chronic pulmonary abscess with a duration of 2 weeks to 3½ years, 20 failed of recovery or satisfactory improvement by bronchoscopy alone. Of the remaining 23 cases, 19 made a complete recovery following bronchoscopic treatment and 4 improved satisfactorily.

### Tuberculous Tracheobronchitis

In a review of the literature on tuberculous tracheobronchitis, Jenks<sup>67</sup> found that little actual progress had been made in the treatment of these lesions in spite of a more general use of the bronchoscope. Ulceration is almost universally treated by some form of cauterization. *Silver nitrate* employed in from 5 to 30 per cent solution as a topical application is most frequently used. Good results have been reported by the use of *electrocautery* alone or in combination with silver nitrate.

The treatment of *bronchostenosis* usually is not satisfactory although temporary improvement may be secured by *dilatation with bougies*. *Ionization of strictures* has been practiced with possibly some benefit. Symptomatic relief from obstruction may be obtained from simple *bronchoscopic aspiration of secretions*. The consensus is against removal of tuberculomas by biting forceps because of the danger of spread of pulmonary disease.

With more frequent employment of bronchoscopy in the study of certain symptoms and signs in tuberculous patients, the recognition of tuberculous tracheobronchitis and the use of direct methods of treatment have received considerable attention. In a study of 516 tuberculous patients, Hawkins<sup>68</sup> found 132 who showed gross evidences of tuberculous tracheobronchitis. In a majority of these, the tuberculous mucosal ulcera-

tions in the tracheobronchial tree healed more readily and with less stenosis when treated with *cauterization* than when untreated.

The occurrence of bronchial stenosis *following thoracoplastic procedures* was observed by Benedict<sup>69</sup> in 3 instances. Gradual *dilation of the stenosed bronchi* and *aspiration of retained secretions* were carried out with marked benefit to the patient. This emphasized the need of bronchoscopic examination of tuberculous patients before thoracoplasty and appropriate treatment to promote healing of bronchial ulceration before operation is undertaken.

Ulceration into the lumen of a bronchus of an actively diseased *tuberculous lymph-node* with little or no calcification is rarely observed. When this does occur there results bronchial obstruction with secondary pulmonary changes. In young children the obstruction may seriously interfere with respiratory function. In the case reported by Vinson and Pembleton,<sup>70</sup> a man, aged 63 years, the clinical and roentgen findings suggested bronchial carcinoma. At bronchoscopy there was found a tumor mass occluding the right lower bronchus. It was *removed bronchoscopically* and found to be a tuberculous lymph-node. Recovery was prompt with practically complete clearing of the right lower lung.

### Bronchial Tumors

1. **Adenoma of Bronchus**—In a study of the literature on vascular adenoma also designated as "*bronchial adenoma*" and "*adenomatous polyp*," Laff<sup>71</sup> found that 5 forms of treatment are available, *viz.*, (1) removal through a bronchoscope; (2) electrocoagulation; (3) radium treatment; (4) roentgen treatment, and (5) partial or total pneumonectomy. The tendency of these tumors to bleed renders bronchoscopic

removal hazardous. Laff instituted *artificial pneumothorax prior to bronchoscopic treatment* in 1 of 3 cases reported by him with gratifying results. Treatment by bronchoscopic methods has resulted in many apparent cures or arrests and should be given a trial. If this proves unsuccessful, *lobectomy* or *pneumonectomy* should be considered.

2. **Carcinoma of Bronchus**—Malignant neoplasms of a bronchus present a far more serious problem from the standpoint of treatment than do benign tumors. While the rôle of bronchoscopy is important in diagnosis, it also is utilized in those cases where irradiation is carried out by roentgen therapy in conjunction with intrabronchially applied radium. In a review of 40 patients with carcinoma reported by Hammond,<sup>72</sup> 6 were treated surgically and 26 by irradiation therapy. None of the 6 patients treated surgically survived the 9-month period. Of the patients treated by a combination of *intra-bronchial radium therapy* and *roentgen therapy* administered externally, 4 apparently have been cured and some prolongation of life and more or less satisfactory palliation for others was obtained.

### Carcinoma of Trachea

The treatment of carcinoma of the trachea is generally difficult and unsatisfactory and the prognosis is unfavorable. *Surgical resection of the trachea, local removal and cauterization with surgical diathermy* carried out through a bronchoscope or through the tracheotomy fistula are the commonly employed methods of treatment. In 2 cases cited by Cann,<sup>73</sup> 1 was treated by *irradiation* and the other by *telerradium* with excellent results. In both cases the tumor disappeared completely and the tracheal obstruction was relieved. Insufficient time, however, had elapsed

since the treatment to permit of final conclusions.

### Foreign Bodies

In a series of 950 consecutive foreign bodies removed endoscopically from the air and food passages reported by Clerf,<sup>74</sup> there were 16 deaths, a mortality rate of 1.68 per cent. Among the factors influencing end-results are the age of the patient, the character and location of the foreign body, its length of sojourn, its effects in the production of pathological changes and previous at-

tempts at removal. Bronchiectasis was found to be the commonest as well as the most serious sequela of bronchial foreign body. Experience has shown that *bronchoscopic removal* of the foreign body, particularly in the case of long sojourn, usually is not adequate to insure complete recovery of the involved lung. Repeated *bronchoscopic aspiration of secretions, removal of granulations, and dilatation of strictures* may be as necessary and important for complete recovery as removal of the foreign body itself. *Lobectomy* may be required.

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## HOARSENESS

By FRANCIS ERNEST LE JEUNE, A.M., M.D.

In the discussion of hoarseness Wells<sup>75</sup> reminds us that the larynx is an organ with a double function. Primarily, it was a part of the organ of respiration and its sole function was to serve as a passageway for air to and from the lungs. When speech was needed, nature, the great economist, instead of creating a new and separate organ, engrafted one upon the already existent respiratory tract which was admirably adapted for the purpose. At the top of the airway, the vocal cords were placed and the lungs were utilized as convenient bellows to throw them into vibration. A good speaking or singing voice depends (1) upon a good formation and healthy condition of the cords; (2) upon a good development of the muscles that activate the cords; (3) upon adequate lung power; (4) upon a favorable development of the resonance cavities of the nose, mouth and throat; and (5) upon the proper methods of articulation.

Hoarseness is so common a symptom of many diseases of the larynx that Negus<sup>76</sup> believes its study entails an

examination of practically all the pathological conditions affecting this organ. The recognition of the cause is of great importance and a full knowledge of the subject is well worth the study of all practitioners.

**Etiology**—Frank<sup>77</sup> has presented a new and interesting systematized classification of the causes of hoarseness, enumerating the frequency with which this symptom is encountered in various disease entities. He further defines hoarseness as an alteration in the speaking voice which results in a roughened or rasping character to the voice and he adds that properly to understand such alteration it is necessary to have a clear conception of the mechanics of voice production.

Voice is produced in the larynx by vibration of the vocal cords, which are set into action by an expiratory current of air from the lungs, very much like the vibrations of an elastic tongue in a reed instrument. In order that the vocal cords may be set in vibration, they first must be put in a state of tension and the

perature of the glottis narrowed to afford resistance to the air current. During speech the cords are brought together by the sphincteric laryngeal girdle and are therefore closed. By virtue of the contraction of the thyroarytenoideus muscles, a certain degree of elasticity is given to the cords. This elasticity varies with the strength and contraction of these muscles. The elasticity of the glottis margins causes the vocal cords to come in apposition during the lowering of pressure, but immediately as they do so the pressure again rises and the cords are blown apart. This escape of puffs of air takes place in a rhythmical manner and thus a musical sound is produced. Aside from the laryngeal mechanism as described, the lungs, cavities of the pharynx, mouth and nose contribute to normal voice production.

Frank<sup>77</sup> further warns that it is not difficult to appreciate that, aside from the local disturbances in the larynx, there can be innumerable causes for disturbances of the voice by any dissociation of the neurogenic hookup from brain to larynx proper, or to other regions that are factors in voice production. Diseases of the upper and lower respiratory tract, systemic diseases, and diseases of the surroundings of the larynx may be responsible for disturbances in the voice. A new classification of the causes of hoarseness is presented with only the main headings given here.

1. Inflammatory (nonspecific).
2. Inflammatory (specific).
3. Trauma.
4. Anomalies.
5. Allergy
6. Metabolic.
7. Associated with skin disorders.
8. Occupational diseases.
9. Benign tumors.
10. Malignant tumors.
11. Neurogenic.
12. Miscellaneous.

From observations by Negus<sup>76</sup> the incidence of hoarseness varies considerably according to the time of life. The various causes of hoarseness are briefly reviewed and special attention is directed to husky voices occurring in young adults. Frequently this may be caused by laryngeal tuberculosis. The pathological cause may be a little more than weakness of the intrinsic laryngeal muscles secondary to a general asthenia, or to a mild catarrhal inflammation of the cords at their posterior extremities. *Functional aphonia* is seen with more frequency in young women and usually responds to *suggestions and reassurance combined with electrical stimulation*. Elderly men with gradually increasing hoarseness must be suspected of having a carcinoma of the vocal cord unless it can be proved otherwise.

**Diagnosis**—The establishment of an accurate diagnosis in a patient presenting the symptom of hoarseness is of the utmost importance. Frank<sup>77</sup> reminds the clinician that the various diseases that are responsible for the production of hoarseness all must be carefully considered and the means of reaching an absolute diagnosis will be, to a great extent, by careful elimination of all possibilities. He further believes that all patients with the symptom of hoarseness should have a thorough examination, to include a complete history and physical examination, laryngoscopy, indirect or direct when the mirror examination is not satisfactory, an x-ray of the chest and occasionally of the neck, Wassermann, complete blood count and urinalysis. Biopsy should be performed when there is the slightest suspicion of a malignancy. When a specimen of tissue is taken for histological examination in a case suspicious of a malignancy, it must be realized that a negative report need not always be conclusive. With the knowledge

that the malignant changes take place in deep cells, it readily can be seen that when a bit of tissue is taken that has not penetrated the depths of the new growth, the pathological report will not reveal malignant changes; however, when a lesion does look suspicious, it is well to repeat the biopsy 1 or more times before excluding the possibility.

Skilled examination will establish a diagnosis. The cause of the vocal disorder may be a simple laryngitis, in which case, a cause may be present in the nose, sinuses, or pharynx; even if this is the case, there still may be malignant

changes commencing in the chronically inflamed mucosa.

**Treatment**—This must be instituted to improve the inflammation in the nose and pharynx and vocal rest, with avoidance of smoking, must be insisted upon for at least 3 weeks.

Benign tumors must be removed with accuracy so as not to produce any distortion of the larynx and vocal cords. Malignant lesions require careful study so as best to determine the proper method of approach so that complete eradication will occur as a result of intervention.

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## PHARYNX AND TONSILS

By WELLWOOD M. NESBITT, B.S., M D.

### Probable Pathogenic Streptococci and Staphylococci in Chronic Low Grade Illness

Using as their criteria of pathogenicity certain *in vitro* tests, Stiles and Chapman<sup>78</sup> made cultures from 395 patients with chronic ailments. The development of these tests has made possible the study of the relation of large numbers of staphylococci and streptococci associated with chronic and acute illnesses.

Of the 395 patients studied, 96.3 per cent had clinical evidence of involvement of the nose or nasopharynx; 52.2 per cent had classic evidence of chronic sinusitis; 44.1 per cent had symptoms of nasopharyngitis. There were 48 cases of tonsillitis or oral infection; bronchitis, 83 cases; colitis, 67; biliary tract, 82; gastroenteritis, 89. Inflammatory conditions of the urinary tract, 38; rheumatoid arthritis in 16; other forms of arthritis in 38. The patients were classified according to the severity of illness, mild or recurrent, moderate, severe or acutely exacerbated.

The oral and nasal cavities and (usually) the feces were tested. The streptococci were mostly of the alpha variety, the staphylococci mostly aureus. Patients with severe symptoms were found more likely to have fecal as well as oral streptococci, and in richer flora. Also, they had a higher ratio of staphylococcus aureus over albus. Acutely exacerbated symptoms were accompanied by a higher proportion of beta streptococci and *Staphylococcus aureus* in the nose and throat. Sinusitis, tonsillitis, and bronchitis were accompanied by a higher ratio of nasopharyngeal streptococci and staphylococci.

The incidence of streptococci was so high that it may be assumed that streptococci are practically universally present in persons with low grade chronic illness. The finding of increased numbers of streptococci in patients with severe symptoms suggests that these organisms may be significant. They may be present in healthy persons and the question arises why these persons should exhibit



TABLE I

RELATION BETWEEN SEVERITY OF SYMPTOMS AND INCIDENCE OF *in Vitro* POSITIVE STREPTOCOCCI AND STAPHYLOCOCCI IN VARIOUS SOURCES

Type of Symptoms	Per Cent of Cases in Which <i>in Vitro</i> Positive Organisms Occurred							
	Streptococci				Staphylococci			
	Nose	Oral Cavity	Feces	Any Focus	Nose	Oral Cavity	Feces	Any Focus
Mild	4.0	96.6	31.6	98.9	64.4	48.3	5.7	71.2
Moderate	9.6	97.6	28.2	98.1	61.5	51.3	6.4	70.5
Severe	13.3	98.7	37.8	100.0	60.0	42.2	6.7	64.4
Acutely exacerbated	10.0	100.0	55.0	100.0	50.0	60.0	0.0	65.0

such varying degrees of health. Varying response to the presence of streptococci might be conditioned by noninfectious factors, by the number and pathogenicity of the streptococci present, by the number of areas infected, and by varying degrees of sensitization to streptococci as demonstrated by Baker, Thomas and Penick.

**Results—*Streptococci***—of 395 patients, 98.7 per cent yielded streptococci. They were found most frequently in the oral cavity (384) and least frequently in the nasal cavity (30). Alpha types were most common in the oral cavity, 96 per cent of the cases. Beta strains were recovered in 9 per cent.

***Staphylococci***—were found in 69.8 per cent of 395 patients. They occurred most frequently in the nose and least in the feces. The albus strains predominated in 44.6 per cent of the cases.

Nasal streptococci are comparatively infrequent, suggesting an inhibiting action of the nasal secretions. Variations seem significant only in regard to the severity, and in cases of colitis and asthma.

Staphylococci were present in about 70 per cent of patients with low grade chronic illness. There was a lower incidence in nonrheumatoid arthritis; otherwise, the incidence was not significantly

varied. A lower incidence of both streptococci and staphylococci was present in osteoarthritis.

### Elongated Styloid Process

This process was found by Fritz<sup>79</sup> to be a relatively common cause of obscure throat complaints. Further, it may project into the tonsillar fossa and interfere with tonsillectomy. Forty-three patients having this condition were found in Duke Hospital. The styloid process extends from the under surface of the petrous portion of the temporal bone forward, downward, and mesially. Many styloid processes that are elongated but still are not long enough to reach the hyoid bone are asymptomatic; but if they project abnormally forward and mesially into the tonsillar fossae, they not only often give rise to symptoms but may interfere with tonsillectomy. The symptoms noted in 43 patients may be summarized as: Fullness in the throat; dysphagia, pain radiating to the mastoid, and soreness of the hard and soft palate, resembling glossopharyngeal neuralgia. The symptoms may increase following tonsillectomy. Diagnosis is by palpating the tonsillar fossae and by x-rays.

Treatment is operative and the set-up is similar to tonsillectomy; the tonsils are first removed if present. The tissues

TABLE II

INCIDENCE OF *in Vitro* POSITIVE STREPTOCOCCI AND STAPHYLOCOCCI WHEN OBSERVATIONS WERE DISTRIBUTED ACCORDING TO CLINICAL DIAGNOSIS

Clinical Group	No. of Cases	Per Cent of Cases in Which <i>in Vitro</i> Positive Organisms Occurred				
		Alpha Streptococci		Staphylococci Any Focus	Staph. Aureus	
		Nose	Feces		Nose	Oral Cavity
All cases	395	4.3	27.1	69.8	44.5	40.3
Sinusitis	206	5.8	25.2	71.8	43.7	42.7
Nasopharyngitis	174	2.9	31.6	65.5	44.2	36.8
Tonsillitis	31	6.5	25.8	83.9	61.3	58.1
Oral infection...	17	11.9	29.4	82.3	47.1	41.2
Bronchitis	83	6.0	21.3	78.7	54.2	45.8
Colitis	67	4.5	<b>47.8</b>	65.6	43.3	43.3
Biliary tract symptoms	82	1.2	33.0	70.7	45.2	41.5
Rheumatoid arthritis	16	0.0	37.5	56.3	43.7	18.8
"Other" arthritis..	38	2.6	23.7	<b>50.0</b>	39.5	31.6
"Rheumatism" ..	52	3.9	38.5	75.0	51.9	42.3
Asthma	22	4.5	<b>54.6</b>	77.3	45.4	40.9
Duodenal ulcer	18	5.6	33.3	55.6	44.4	16.7

Note—Because other groups of organisms showed little variation, only alpha streptococci in nose and feces, total staphylococci, and *Staph. aureus* in nose and oral cavity are tabulated.

The percentages in bold face type are statistically significant.

over the elongated styloid process are then stripped back and the presenting tip is amputated with a rongeur, the proximity of the carotid artery and the glossopharyngeal nerve being kept in mind. Of 11 cases, **amputation** of the process removed the symptoms. Of 32 others, 50 per cent did not have symptoms, the remainder not coming to operation for various reasons. The author was "impressed by the preponderance of the condition in the female sex as compared with the male."

### Tonsillectomy

Infected tonsil remnants and other hypertrophied pharyngeal lymphoid tissue after tonsillectomy are emphasized by Campbell<sup>80</sup> as the cause of continued symptoms.

A statistical study of the pharynx of 887 girls between the ages of 18 and 21 years was made at the University of Pennsylvania. An outline of the results

obtained revealed only 30 per cent of the students had not had their tonsils removed. Of the 621 students who had been operated on, 77.3 showed tonsillar remnants in the fossae. Of these 66.6 per cent were placed in the class of non-infected remnants and 10.6 per cent in the class of infected remnants. Of the 103 students who had been operated on by otolaryngologists, 74.7 per cent showed tonsillar remnants, 14.5 per cent showed scars, and 25.3 per cent had no lymphoid tissue in the tonsillar fossae. Of the 44 students operated on by family physicians, 79.5 per cent showed tonsillar remnants, 40.9 per cent showed scars, and 20.5 per cent had fossae free from lymphoid tissue.

The writer quotes many reports of other similar investigations which show rather consistent results. Rhoads and Dick examined 403 nurses entering training at Presbyterian and Cook County hospitals and found tonsillar tis-

sue remaining in 73 per cent of tonsillectomized students. These authors made bacterial counts on the tonsillar stump and found that the stump harbored more pathogenic bacteria per gram than tonsils removed for the first time.

Campbell attributes incomplete removal to (1) improper anesthetic administration; (2) inadequate illumination of the operative field; (3) unskillful assistance at the operation; (4) imperfect inspection of the fossae. Proper anesthesia, illumination and assistance are the important factors in detecting small pieces of lymphoid tissue that have escaped the surgical technic.

In addition, recurrence of tissue does occur by (1) actual regrowth of lymphoid tissue, (2) proliferation of a lymph-node in the fascia, (3) hypertrophy of the lymphoid tissue in the retained plica triangularis, and (4) extension of the lingual tonsil into the lower pole of the fossa.

Previous practice of leaving in place the triangular, supratonsillar, and retrotonsillar plicae, in view of the demonstrated lymphoid tissue present in them,

has led to a recurrence of tonsillar tissue in the lower part of the fossa in a large percentage of cases. All lymphoid tissue in the throat tends to hypertrophy after tonsillectomy, and the lingual tonsillar hypertrophy may fill up half or more of the lower tonsillar bed.

It is emphasized that the well performed tonsillectomy is not a simple operation, and this is borne out by the great preponderance of scarring when it is not done by specialists. Destruction of the posterior pillar may impair the function of the eustachian tube and of swallowing, and cause retractions of the soft palate, resulting in speech defects. Contraction and even atresia of the nasopharynx may follow injury to the pillars and palate.

The study does emphasize that recurrence of tonsillar tissue which has hypertrophied following operation is often responsible for the continuation of the symptoms which necessitated the tonsillectomy and often give more local discomfort and symptoms referable to a focus of infection than were caused by the original tonsil.

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## RETROPHARYNGEAL ABSCESS

By SAMUEL IGLAUER, B.S., M.D.

**Clinical**—Rimer<sup>81</sup> gives an excellent analysis of 140 cases of retropharyngeal abscess which were observed over a period of 26 years. The first presenting symptom is usually dysphagia, which appears within 5 to 20 days after the onset of an acute upper respiratory infection. Increasing dyspnea is a later symptom as the abscess presses forward and downward. In the experience of Rimer and his coworkers, many of these abscesses were diagnosed and treated as laryngeal diphtheria. This was particularly true

in the first 36 cases, 32 of which were treated for diphtheria prior to their admission. In these 36 cases the average duration of sickness before the diagnosis and drainage of the abscess was 19½ days, whereas in the remaining cases the average duration of sickness was 12 days. All the cases reported were opened and drained through the mouth. Rimer and his coworkers believe that the difference between 19½ and 12 days of sickness accounted for the difference between the mortality of 30 per cent in the first 36

cases and that of 6.7 per cent in the last 104 cases. In the whole series the average mortality was 12 per cent.

[In the opinion of the Reviewer the total mortality rate quoted is considerably higher than among the cases usually encountered in hospital practice.]

**Anatomic**—In recent years much attention has been paid to the anatomic site and the localization of purulent collections external to the pharynx. In this connection, Grodinsky<sup>82</sup> lays great stress on the "alar" fascia (a fourth layer of cervical fascia), which he describes as "extending across the midline posterior to the pharynx, esophagus, and visceral fascia, after which it fuses with the prevertebral fascia at the tips of the transverse processes to which both these layers are attached." The alar fascia terminates laterally in the carotid sheath of which it forms an important part. "Posteriorly, between the transverse processes, the alar fascia extends from the base of the skull to about the level of the seventh cervical vertebra where it becomes intimately fused with the visceral fascia."

According to Grodinsky's interpretation, there are 4 areolar spaces posterior to the pharynx, *i. e.*, a space between the pharyngeal wall and the visceral fascia (visceral space); 2 spaces, right and left, between the visceral and the alar fascia; and, finally, the space between the alar and the prevertebral fascia (postvisceral space of the older anatomists). Any one of these spaces might be the site of an abscess. Infection in the visceral space, as well as infection in the space between the visceral and alar fascia, would tend to remain localized, but the postvisceral space is the "danger space" from which infection is apt to gravitate into the posterior mediastinum. According to Pearse,<sup>83</sup> this particular space consti-

tutes the pathway of infection in 71 per cent of descending cervical infections.

Weintraub<sup>84</sup> has also described 3 areolar tissue spaces external to the pharynx musculature. From within outward there is a right and left closed intramural "peripharyngeal" space with a fibrous, median, vertical septum between the 2 spaces. Behind these there is a sin-

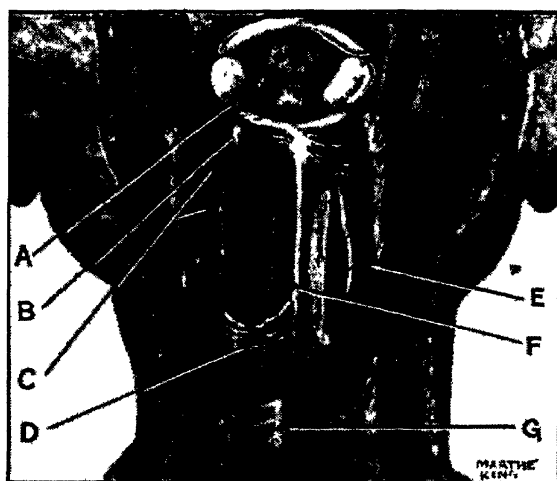


Fig. 1 — Neck of newborn infant viewed from behind. *A*, Indicates the atlas; *B*, the lateral retropharyngeal lymph gland; *C*, a chain of fat; *D*, the left peripharyngeal space, laid open; *E*, the right peripharyngeal space, partially opened; *F*, the fibrous septum between the peripharyngeal spaces; and *G*, the esophagus (Iglauer Arch. Otolaryngol.)

gle, large, median, retropharyngeal space continuous below with the retroesophageal space. These latter spaces together constitute the postvisceral space. The paired peripharyngeal spaces apparently correspond to the 2 alar fascial spaces described by Grodinsky.

**Pathology**—Iglauer<sup>85</sup> has called attention again to the intimate anatomic relation of the lateral retropharyngeal lymph-glands to the peripharyngeal space. He is of the opinion that when these lymph-glands break down, the infection is discharged into the adjacent peripharyngeal space (Fig. 1) and is usually pocketed in this space, giving rise

to the common retropharyngeal abscess. In this connection he points out that the anatomic site of the peripharyngeal space is practically identical with the clinical site of the abscess. For this reason the term, "*peripharyngeal*" abscess would be more accurate than the term, retropharyngeal abscess. The latter term should be reserved for infection in the postvisceral space. Should the peripharyngeal abscess rupture out of its confines, it would tend to invade the adjacent postvisceral "danger" space or the parapharyngeal space. In the diagnosis of retropharyngeal infections, lateral roentgenograms of the neck will give valuable information as to the localization or spread of the abscess.

*Treatment* — The ordinary *uncomplicated abscess* should be *opened through the mouth*, but an *abscess extending into the parapharyngeal or postvisceral space* usually demands an *external approach*.<sup>6</sup>

#### Petrositis and Retropharyngeal Abscess

In the otologic literature there have been occasional reports of clinical cases

of petrositis complicated by abscess formation behind the pharynx, but, according to Podesta,<sup>86</sup> the literature is wanting in serial histological autopsy studies of such cases. This author describes in detail the histopathologic findings in a case of gravitating "retropharyngeal" abscess taking its origin from an osteomyelitis in the occipital and temporal (petrous) bones. The osteomyelitis was secondary to an exacerbation of a chronic suppurating ear in the case of a 12-year-old boy. The pathway of the abscess could be traced from infected foci located chiefly in the body of the occipital bone posteriorly and the prevertebral muscles and ligaments anteriorly. It was situated immediately behind the base of adenoid vegetations and did not gravitate beyond the rhinopharynx.

[Reviewer's Note: Podesta's sections are very interesting and instructive. In a sense this was not a true retropharyngeal abscess, since it did not invade the areolar tissues of the retropharyngeal spaces. It did, however, resemble a prevertebral abscess such as occurs with caries of the uppermost cervical vertebrae.]

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## PHYSICAL THERAPEUTIC PROCEDURES IN OTOLARYNGOLOGY

By ABRAHAM R. HOLLENDER, M.D.

During the past few years an increased amount of experimental and clinical research with physical therapeutic procedures has made it necessary to re-evaluate some of them in ear, nose and throat diseases. Clinical trials with short-wave diathermy, for example, have not borne out the earlier enthusiastic claims for the use of heat in certain forms of nasal sinusitis. While heat has always been employed in the treatment of in-

flammatory processes, and has been advocated more or less at random in all types of nasal sinusitis, the time has come when such empiricism is no longer justified.

X-rays, too, have been employed extensively in the nonsurgical treatment of nasal sinusitis. There is no doubt that they have a definite place in the management of certain rhinologic affections, but, like short-wave diathermy, it behooves the

scientific worker to rationalize their application.

The present status of short-wave diathermy and the x-rays in the treatment of nasal sinusitis will be considered.

### Short-wave Diathermy

For deep heating effects, short-wave diathermy continues to be the procedure of choice. It is unquestionably the most effective thermotherapeutic agent as compared with other available methods of conveying external heat to the body. In spite of this, in nasal sinusitis the results have not been such as to encourage its general use in rhinologic practice.

Short-wave diathermy is applied (1) with an electric field, air-spaced or insulated electrodes being used; (2) with an electromagnetic field method, a cable being employed. From a clinical standpoint, so far as the accessory nasal sinuses are concerned, it seems to make little or no difference whether air-spaced, rubber condenser electrodes or the electromagnetic field with cable are used. The main difference lies in technical application. Treatment of any of the nasal sinuses is greatly facilitated by the use of air-spaced electrodes fixed to flexible arms attached to the cabinet framework of the apparatus. The frontals and maxillaries lend themselves to this treatment without difficulty, but as with conventional diathermy, the posterior sinuses are little if at all influenced by short-wave procedures. Whether heating of the posterior sinus areas can be effected has not been proved experimentally. Clinical trials in large series of cases have failed to show improvement either in the acute, subacute or chronic forms of ethmoiditis or sphenoiditis.

The main advantage obtained from short-wave diathermy is the indisputable fact that it creates heat at much greater

depths than was possible with conventional diathermy, and that bony structures which present an almost insurmountable obstacle to the penetration of the longer waves are easily passed through by the short waves. Considering the osseous structure of the head and face, it is evident that the treatment of sinusitis should be rendered more effective by the added use of short-wave diathermy.

While short-wave diathermy can be safely applied to empyemic conditions of any of the sinuses, claims of European workers that surgical intervention is obviated have not been substantiated. The tendency to employ diathermy alone in the treatment of nasal sinusitis is objectionable. When a pathologic process is such that it obviously can be eradicated only by operation, precious time will be lost in seeking to obtain relief from non-surgical therapy. In spite of what has been said regarding the applicability of short-wave diathermy to acute suppurative processes, drainage should be established in every case at the proper time.

It has been found that in most instances local tissue temperature is not appreciably elevated or elevated only slightly when diathermy is applied to any of the sinuses, especially the maxillary sinus. The opinion has been expressed that topical heat is of definite value despite the drop in temperature, the phenomenon being apparently a part of the mechanism involved in the regulation of the temperature of the body.

Clinical studies have demonstrated 3 important facts in connection with the use of short-wave diathermy in acute and chronic nasal sinusitis.

1. Short-wave diathermy is not in itself sufficiently effective in the treatment of acute sinusitis to be employed to the exclusion of other recognized therapeutic procedures.

2 Short-wave diathermy is not a curative method of treatment of chronic sinusitis, when used either alone or in combination with other nonsurgical measures

3 Short-wave diathermy is an effective aid to indicated accepted procedures in cases of acute sinusitis, hastening the abatement of symptoms and shortening the course of the disease.

The observation has also been made that allergic sinusitis and hyperplastic sinusitis are contraindications to local heat in any form. Short-wave diathermy as a postoperative aid has been disappointing, demonstrating more conclusively the futility of applying this agent in chronic sinusitis. It is probable that short-wave diathermy fails in chronic sinusitis because of fixed tissue changes which do not yield to most local nonsurgical procedures.

### X-ray Therapy

The rationale of roentgen therapy in nasal sinusitis has been explained in several ways. According to Butler and Wooley, it is based on the early influx and destruction of lymphocytes with the liberation of the antitoxic substances that they are thought to contain, together with early appearance of macrophages in greater numbers, intensifying the usual reaction to the infection and hastening repair. "This explains the reaction that occurs several days following treatment. The patient usually notices an increase in nasal discharge and other sinus symptoms, beginning a few days after treatment and lasting 3 or 4 days."

Too much should not be expected from x-ray treatment of nasal sinusitis. In some respects the x-rays have an effect on acute or subacute sinusitis similar to short-wave diathermy, *i. e.*, relief of pain, provided adequate drainage has been established. Reliance on x-ray therapy alone to cure sinusitis has met with disappointment. In this connection, treatment by a roentgenologist without the co-operation of a rhinologist, who is more competent to judge results, should be discouraged.

While reports are at variance, strong evidence is available to disprove the value of x-ray therapy in *chronic* nasal sinusitis. The contention that frequently there is marked clinical improvement without complete disappearance of sinus symptoms cannot be accepted as accurate. Such improvement has occurred intermittently without any therapy. To attribute it to any special treatment, without suitable controls, would create considerable controversy. The fact remains that in most instances radiographic improvement in chronic nasal sinusitis is lacking. It is not disputed that when skillfully applied, roentgen treatment does no harm and causes no serious reactions.

Evaluation of the roentgen treatment of nasal sinusitis may be summarized thus:

1. Irradiation is a useful adjuvant in acute or subacute sinusitis in which drainage is free or has been adequately established.

2. X-ray therapy may hasten healing.

3. It is doubtful whether favorable influence may be produced in the large majority of cases of chronic sinusitis, or that it will replace surgery in the management of this condition.

4. Irradiation should be accorded a place in the treatment of selected cases of acute and subacute sinusitis, but co-operation between the roentgenologist and the rhinologist is essential for scientific application and the checking of progress.

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scientific worker to rationalize their application.

The present status of short-wave diathermy and the x-rays in the treatment of nasal sinusitis will be considered.

### Short-wave Diathermy

For deep heating effects, short-wave diathermy continues to be the procedure of choice. It is unquestionably the most effective thermotherapeutic agent as compared with other available methods of conveying external heat to the body. In spite of this, in nasal sinusitis the results have not been such as to encourage its general use in rhinologic practice.

Short-wave diathermy is applied (1) with an electric field, air-spaced or insulated electrodes being used; (2) with an electromagnetic field method, a cable being employed. From a clinical standpoint, so far as the accessory nasal sinuses are concerned, it seems to make little or no difference whether air-spaced, rubber condenser electrodes or the electromagnetic field with cable are used. The main difference lies in technical application. Treatment of any of the nasal sinuses is greatly facilitated by the use of air-spaced electrodes fixed to flexible arms attached to the cabinet framework of the apparatus. The frontals and maxillaries lend themselves to this treatment without difficulty, but as with conventional diathermy, the posterior sinuses are little if at all influenced by short-wave procedures. Whether heating of the posterior sinus areas can be effected has not been proved experimentally. Clinical trials in large series of cases have failed to show improvement either in the acute, subacute or chronic forms of ethmoiditis or sphenoiditis.

The main advantage obtained from short-wave diathermy is the indisputable fact that it creates heat at much greater

depths than was possible with conventional diathermy, and that bony structures which present an almost insurmountable obstacle to the penetration of the longer waves are easily passed through by the short waves. Considering the osseous structure of the head and face, it is evident that the treatment of sinusitis should be rendered more effective by the added use of short-wave diathermy.

While short-wave diathermy can be safely applied to empyemic conditions of any of the sinuses, claims of European workers that surgical intervention is obviated have not been substantiated. The tendency to employ diathermy alone in the treatment of nasal sinusitis is objectionable. When a pathologic process is such that it obviously can be eradicated only by operation, precious time will be lost in seeking to obtain relief from non-surgical therapy. In spite of what has been said regarding the applicability of short-wave diathermy to acute suppurative processes, drainage should be established in every case at the proper time.

It has been found that in most instances local tissue temperature is not appreciably elevated or elevated only slightly when diathermy is applied to any of the sinuses, especially the maxillary sinus. The opinion has been expressed that topical heat is of definite value despite the drop in temperature, the phenomenon being apparently a part of the mechanism involved in the regulation of the temperature of the body.

Clinical studies have demonstrated 3 important facts in connection with the use of short-wave diathermy in acute and chronic nasal sinusitis.

1. Short-wave diathermy is not in itself sufficiently effective in the treatment of acute sinusitis to be employed to the exclusion of other recognized therapeutic procedures.



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## PEDIATRICS

*Edited by* A. GRAEME MITCHELL, M.D.

### ANEMIAS IN CHILDREN

*By* CLARE R. RITTERSHOFER, A.M., M.D

**Anemias of Early Infancy**—In a review of the anemias of the newborn period Carl Smith<sup>1</sup> divides these anemias on a chronological basis into 2 categories. The first group appears in the earliest days of the neonatal period and includes erythroblastosis fetalis, hemorrhagic disease of the newborn, and a miscellaneous group of anemias associated with sepsis and infection, which includes congenital syphilis. The second group comprises the condition referred to variously as erythroblastic, Cooley's or Mediterranean anemia, familial hemolytic jaundice, and hypoplastic anemia.

*Erythroblastosis fetalis* is a symptom complex consisting of hydrops fetalis, icterus gravis, and anemia of the newborn. They have certain common features: severe grades of macrocytic and hyperchromic anemia, the fetal type of extramedullary hematopoiesis (erythroblastosis), abnormal numbers of nucleated red cells in the circulating blood (erythroblastemia), edema, jaundice, and the fact that successive newborn siblings may be affected by one or the other of these conditions. Yellow vernix caseosa and amniotic fluid may pre-  
 sage the development of one of the forms of this disease, but the association is by no means constant.

In *hydrops fetalis* and *icterus gravis* the placenta, the liver, and the spleen are notably enlarged. In hydrops fetalis the edema is the most striking feature while in icterus gravis it is the intense jaundice, although both signs occur in each condition. In icterus gravis the reticulocytes are increased; in severe cases the nucleated red cells may reach levels of 50,000 and more per cubic millimeter and may not disappear from the circulation for several weeks. In addition there may be an exaggeration of the normal leukocytosis present at birth and the appearance of large numbers of immature cells of the myeloid series and occasionally even myeloblasts.

The features possessed by the other members of the triad are evidence in least degree in the cases of anemia of the newborn. Here the anemia, which is sudden and severe, is noted at a variable time during the first 2 weeks; extramedullary hematopoiesis is inconstant, while nucleated red cells may be absent or only slightly increased and then not until the onset of recovery. The reticulocytes may be increased at the onset and during recovery. Jaundice is mild or absent and is explained by the functional ability of the liver to excrete the bile pigments which have

been formed. The gradation of one member of this group into another has been repeatedly demonstrated by cases of icterus gravis with severe edema, and by milder cases of this condition which, during the recovery phase, are almost indistinguishable from congenital anemia. It is frequently impossible to separate congenital anemia of the newborn from less severe cases of icterus gravis when the anemia in its early stages is associated with transitory jaundice and erythroblastemia. The clinical and hematologic manifestations of erythroblastosis fetalis may be interpreted in part at least as disturbances of varying grades of severity due to deficiencies of one or more factors which normally regulate and assure the orderly processes of hematopoiesis. These principles normally originate in the fetus, continue to be elaborated in sufficient quantities in normal newborn infants, and are probably supplemented by a supply from the mother. Inadequacies of the latter component may explain the familial nature of this syndrome.

Shapiro and Cohen<sup>2</sup> report the occurrence of anemia of the newborn in an identical twin and universal edema of the newborn in the other, with survival in both cases. An important factor in saving the life of the twin with edema was the *blood transfusion* which was given 6 hours after birth. The authors believe that the frequency of transfusions should be guided by the clinical and hematologic picture presented by the patient and not determined arbitrarily. Large doses of liver extract administered intramuscularly failed to halt the increasing anemia. Human blood serum caused no appreciable change in the anemia.

Dwyer and Neff<sup>3</sup> reported a case of anemia of the newborn in whom erythroblastosis and icterus were not

present and which did not respond to repeated transfusions. The use of *liver extract* subcutaneously was followed by the appearance of reticulocytes and immature granulocytes immediately, with a gradual return to normal blood values.

Kirmilidis<sup>4</sup> groups icterus gravis, hydrops universalis, and anemia neonatorum in a triad of primary idiopathic congenital anemias. The author claims that the term fetal erythroblastosis is not entirely correct because erythroblastosis may be absent. In 2 cases described by him both recovered following *transfusions* and *liver therapy*.

**Anemia Associated with Infection and Sepsis**—In the newborn period a varied blood picture is observed in infection depending upon its severity according to Carl Smith.<sup>1</sup> Infection often results in a fetal type of blood picture with an outpouring of nucleated red cells and of immature white cells, due to a lag in the shift from fetal to extrauterine hematopoiesis. The newborn infant with *congenital syphilis* may show this picture together with jaundice, anemia, an enlargement of the liver and spleen, and a tendency to hemorrhage. Serologic tests and roentgenograms of the long bones differentiate it from icterus gravis. Jaundice and bleeding may occur in the course of sepsis and are more commonly associated with staphylococci and *B. coli* than with streptococci. Anemia is more frequent, however, with streptococcus and *B. coli* septicemia than in that caused by the staphylococcus. *Winkel's disease* is a severe form of hemolytic anemia which is probably due to infection and is associated with cyanosis, icterus, and hemoglobinuria. The onset of this condition as well as of other forms of sepsis does not occur until about the third or fourth day of life or at a later day in the first 2 weeks of life.

**Hypoplastic or Chronic Congenital Aregenerative Anemia** — This anemia, which resembles aplastic anemia, has been noted in the latter part of the neonatal period. The clinical course and the blood picture lack the severity and acuteness of this condition and it has therefore been regarded as one of its variants to which the term hypoplastic anemia has been applied. This anemia is an aregenerative type, congenital, characterized by a marked reduction in hemoglobin and red cells, and is distinguished from aplastic anemia by its chronic course, and by the absence of hemorrhage. The platelets and the total number of leukocytes and reticulocytes are only slightly or moderately decreased, and the percentage of each type of white cell is normal. The smear shows an absence of immature white or red cells, and the coagulation, bleeding time, clot retraction, and fragility tests are normal. Hypoplastic anemia should be considered when, despite adequate antianemic therapy, including frequent transfusions, hemoglobin, red cells and reticulocytes remain at low levels. This anemia continues into late infancy and childhood and is not influenced by any form of antianemic therapy except *transfusions*, which must be carried out at frequent intervals to sustain life.

**Congenital Nutritional Anemia** — According to Carl Smith<sup>1</sup> it has been generally accepted that infants born of mothers who have suffered from iron deficiency during pregnancy showed a normal blood picture at birth and that the influence of inadequate storage did not become manifest until later in the first year. Exceptions to this principle have been noted, however, in the cases of nutritional anemia observed at birth or soon after, which were identical with nutritional anemia in older infants. The

infrequency of congenital iron deficiency anemia despite deficiency of iron in maternal tissues attests to adequate transfer of hematopoietic substances from mother to fetus, sufficient at least in amount to tide the infant over the early period of insufficient iron intake.

Congenital nutritional anemia must be differentiated from other members of the group of erythroblastosis fetalis. There is usually a history of pallor from birth, but there is no jaundice, no sudden and pronounced drop in both red cells and hemoglobin, and reticulocytosis is absent before treatment is begun. Although the red cells may be moderately reduced, the reduction is usually in hemoglobin alone so that the anemia is hypochromic rather than hyperchromic, as is the case in erythroblastosis fetalis. The administration of *iron* in congenital nutritional anemia results in recovery with an associated reticulocyte response.

**Anemia of Prematures and Post-infectious Anemias**—Gobell<sup>5</sup> reported that there was a definite effect produced by nicotinic acid amide and riboflavin in anemias of prematurity, and that in postinfectious anemias an increase of hemoglobin and red cells resulted in a short time after the use of *suprarenal cortical extract* and *nicotinic acid amide*.

**Iron Deficiency Anemia** — In a study of 883 rural school children in Florida, Abbott and Ahmann<sup>6</sup> showed that 50 per cent of these children were anemic and 31 per cent had borderline anemia. Many of the children did not show alarming symptoms of anemia until the hemoglobin was reduced as much as 50 per cent. A number of these children had been born of anemic mothers and probably had been anemic in some degree for the greater part of their lives. The most pronounced

symptoms of anemia are pallor, general muscular weakness and faintness. The color and texture of the mucous membranes offer the most reliable criteria for diagnostic purposes. In severe anemia the mucous membranes of the lips are spongy and yellow, with marked paleness throughout the entire oral cavity. The administration of *iron* and *ammonium citrate* in adequate amounts over 42 days resulted in a rapid regeneration of hemoglobin, but diet alone, even after 90 days, did not restore the hemoglobin to normal levels when the initial values were less than 50 per cent.

Wilbar<sup>7</sup> reported the presence of an iron anemia of considerable degree among the children of the sugar plantations of Hawaii and its treatment by means of a *cane juice concentrate* which could be used in infant formulas for infant feeding. This carbohydrate contains 1 to 3 mg. of iron per 100 cc. of cane syrup. The iron is entirely soluble and nearly all of it is in the ferrous state, so that all of the iron should be available for use in the body. A distinct added advantage would be its cheapness, as nutritional anemia seems to be prevalent mainly among children of families of meager income.

Wilson<sup>8</sup> attempted to show the relationship of *achlorhydria* to the nutritional anemia of children by stabilizing the reticulocyte count while under observation, then by giving HCl by mouth, and finally by watching the reticulocyte response. The results suggest that acid replacement therapy will not cause an immediate response of the marrow by the production of reticulocytes. The clinical evidence that *achlorhydria* is causally related to the anemia is confirmed, but it still remains to be shown if continuous treatment with acid would improve the absorption of the iron in

the diet and so improve the anemia. Evidently the hematinic effect of the acid is so slight as to be of no therapeutic value in this disease.

Crowley and Taylor<sup>9</sup> state that a mild iron resistant hypo- or orthochromic anemia, associated with latent low-phosphorus rickets, was found among 12 school children aged between 6 and 12 years. The low blood phosphorus is rapidly corrected by massive doses of *vitamin D*, but the anemia is relieved only by a combination of *iron and vitamin D*. A combination of *vitamin D* in doses of 200,000 international units given at fortnightly intervals and *ferrous sulfate*, 5 grains (0.3 Gm.) twice a day, raised the hemoglobin to a satisfactory level in 1 month.

Garsche<sup>10</sup> reported a case of essential hypochromic anemia in a child in whom the diagnosis was made possible by the finding of a high grade non-healing iron deficiency anemia with gastrointestinal symptoms, such as hyp acidity, accelerated peristalsis of the small intestine, dysphagia with esophageal spasm and atrophy of the pharyngeal mucous membranes.

**Copper in Iron Deficiency Anemia**—According to Hutchinson,<sup>11</sup> after a review of the rôle of copper in iron deficiency anemias of children, it is rational to introduce some *copper* in all iron medications used for the treatment of this type of anemia.

**Relation of Vitamin C Deficiency to Nutritional Anemia**—Aron<sup>12</sup> studied the relationship of ascorbic acid to blood formation and to anemia in guinea-pigs and found that guinea-pigs made anemic by the withdrawal of ascorbic acid from their diet can be cured by the administration of *ascorbic acid* in large amounts either orally or subcutaneously. This cure, however, is successful only in animals which have

lost not more than about 25 per cent of their body weight. This indicates that the anemia is cured long before the repair of the other body tissues is accomplished.

**Iron Metabolism in Infancy**—Josephs<sup>13</sup> studied the iron balance in a large number of infants for the purpose of ascertaining the factors influencing the retention of iron on milk and cereal diets. On the average, approximately 60 per cent of the iron taken in with the food was absorbed. Retention of iron tended to be below the average normal during infections, and in infants not receiving vitamin D. In cases of infection the diminished retention seemed to be due to the reduction in intake caused by the loss of appetite, while in cases of vitamin D deficiency there appeared to be an actual diminution of iron absorption.

The same author<sup>14</sup> studied for short periods infants varying in age from 3 weeks to 20 months, some normal, some suffering from nutritional anemia. He concluded that retention of iron is enhanced when the intake is above a level of 2 mg. per kilogram of body weight per day. The factor having the greatest influence on the reticulocyte rise is the initial hemoglobin level. Below 6 months of age, utilization depends almost entirely upon age or rate of growth. Above 6 months, utilization depends to a considerable extent upon retention. Iron that is taken into the body is utilized for hemoglobin formation only after the lapse of several days, *i.e.*, "storage" precedes utilization. Medicinal iron has an important "regulatory" function in addition to that of supplying a building stone for hemoglobin.

**Erythroblastic or Cooley's Anemia**—According to Carl Smith,<sup>1</sup> the blood smear of this anemia in the early

stages shows few distinctive features. The large increase in nucleated red blood cells which characterized the blood in advanced cases, is not observed early, but makes an appearance as the anemia progresses. An unexplained leukocytosis in the latter part of the neonatal period accompanied by moderate numbers of immature myeloid cells may attract attention to the onset of this disease. The liver and spleen are not enlarged beyond that of normal infants, but in the course of the neonatal period a slight increase in size and firmness of the spleen is noted.

The span of fragility of the red cells is prolonged and this property may be noted in adult relatives in whom the disease is latent and unsuspected. An important diagnostic feature of this condition is its racial limitation to children, one or both of whose parents were born in Mediterranean countries. The characteristic bony changes produced by marrow hyperplasia and reflected in the roentgenogram are usually not observed for many months following the neonatal period, when the anemia has become progressive. In like fashion, the muddy yellow pigmentation of the skin and the mongoloid facies produced by changes in the skull bones are not observed until the anemia has persisted for some time.

In addition to erythroblastosis, the red cells manifest polychromatophilia, poikilocytosis and anisocytosis. For diagnostic purposes the most important cells are macrocytic cells which appear in great numbers and whose size is sometimes of unusual proportions. Three types of macrocytic red cells characterize the blood of advanced cases of Cooley's anemia, especially following splenectomy. All types possess abnormal thinness. One of these is a non-specific type, called a target corpuscle, because of its deeply stained center and

periphery arranged in concentric light and dark zones. The central dense, dot-like area may be connected to the periphery by an irregular band of hemoglobin. The second type is a round or oval cell, with narrow rim of hemoglobin of varying thickness, with a large area of central achromia in which a faintly stained island of hemoglobin may be discerned. The third type is a large, pale erythrocyte which contains irregularly distributed hemoglobin which is clumped. This cell is extremely thin and leaf-like. Ridges are sometimes produced by wrinkling within the cell.

**Relation Between Anemias and Digestive Diseases in Children** — Kugelmass<sup>15</sup> reports that the anemias associated with diseases of the gastrointestinal tract may be macrocytic, microcytic, or normocytic. *Macrocytic anemia* develops when the supply, absorption, or use of the erythrocyte maturing factor, E. M. F., is deficient. Macrocytosis is characteristic of this anemia. The cell diameter is between 8 and 10 micra. Chronic intestinal obstruction may produce a macrocytic anemia because the resultant vomiting and diarrhea interfere with the ingestion of the extrinsic factor and with the absorption of the E. M. F. In these cases there is need for a bland low-residue diet rich in *liver extract*, or the administration of *erythrocyte maturing factor* by injection. Celiac disease may be complicated by a macrocytic anemia because of the deficient absorption of the E. M. F. from the small intestines aggravated by the diarrhea. Sprue produces a macrocytic anemia, partly because of the dietary deficiency in the extrinsic factor and partly because of the deficient absorption of the E. M. F. from the small intestine.

*Normocytic anemia* develops from an acute external or internal hemor-

rhage from the gastrointestinal tract, from internal blood destruction from hemolytic poisons and intestinal parasites, and from deficiency diseases.

*Hypochromic microcytic anemia* develops as a result of a deficiency in iron, copper or protein. Chronic hemorrhage in ulcerative colitis, amebic dysentery, Meckel's diverticulum, etc., produces a microcytic anemia because of the loss of iron from body reserves, but the administration of adequate doses of *iron* corrects the anemia despite continued loss of blood.

Iron deficiency in alimentary allergy produces a microcytic anemia because of protein restriction, thus limiting iron-containing foods. The administration of inorganic iron as a dietary supplement clears the anemia. Proper feeding by *gavage*, with added *inorganic iron salts*, corrects the anemia.

**Circulatory Function in Anemia** — Parsons and Wright<sup>16</sup> summarized their study of various aspects of cardiac function in 5 anemic children, of whom 4 had been anemic for 3 or more years, as follows:

(1) The function of the heart is adversely affected by anemia. Changes are maximal in anemia of long duration and minimal in moderate anemia of short duration.

(2) An increase of cardiac output is the most important compensatory mechanism in the anemic patient.

(3) Simple indications of cardiac reserve, such as the response of pulse, respirations, and blood-pressure to a given amount of exercise, may be highly misleading in the estimation of degrees of cardiac embarrassment.

(4) Treatment of anemia leads to improvement in cardiac function, the amount of recovery being inversely related to the duration of the disease.

**Macrocytic Hyperchromic Anemia in Children** — Magnusson and Hamne<sup>17</sup> describe a case of macrocytic hyperchromic anemia in celiac disease in a girl of 8½ years who presented 5 years earlier a clinical picture which was typical of celiac disease combined with anemia. Blood smears taken at the height of the anemia showed normoblasts and macroblasts but no megaloblasts. Sternal puncture failed to reveal any megaloblasts even though other findings suggested pernicious anemia. The patient responded to *ferrous chloride* and a *banana and apple diet*.

**Anemia in Nephritis**—Cass<sup>18</sup> studied 120 cases of nephritis in the Children's Hospital, Birmingham, England, and grouped them in healed, latent, active or terminal stages. These were investigated for anemia. In the acute initial attack the anemia was slight, tended to recover spontaneously and was probably due to the infection associated with nephritis. In a few cases there was evidence of mild hypochromic anemia, probably due to a combination

of hematuria and restricted diet. No anemia was found in the presence of sepsis. In the terminal stage, anemia was found to be a late complication and was nearly always accompanied by marked nitrogen retention.

**Leukocytes in the Blood in Severe Anemias of Infancy** — Nobécourt<sup>19</sup> studied 23 cases of anemia in which the red cells numbered less than 3 million red blood corpuscles and concluded (1) that with a moderate anemia of 2 to 3 million red blood corpuscles, 2 groups of anemias must be distinguished, *i. e.*, (a) the group in which the leukocytes appear in normal numbers, with the granulocytes predominating over the lymphocytes; (b) the group in which there are changes in the leukocyte count, which may be above or below the average, but with a constant predominance of the lymphatic types over the granulocytic; (2) that in cases of severe anemia with a red cell count below 2 million, the number of white cells is never normal; it may vary from 3,000 to over 60,000.

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## CHICKENPOX

By ROBERT A. LYON, M.D.

**Etiology**—Two small epidemics of chickenpox following the exposure of children to herpes zoster have been reported by Blatt, Zeldes and Stein.<sup>20</sup> In 1 instance a child developed chickenpox 13 days after exposure to a patient with herpes zoster. In the second

instance a nurse who had herpes zoster seemed to have been responsible for the exposure of 2 children who developed chickenpox 14 and 18 days later. The authors observed that numerous other children who were exposed to the herpes zoster did not contract chickenpox.

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## DIABETES MELLITUS IN CHILDREN

By WALDO E. NELSON, M.D.

**Growth and Development**—Interesting observations concerning the development of the diabetic child have been presented by Brown and Thompson.<sup>21</sup>

Data pertaining to body growth, intelligence, heredity, sex distribution, and incidence of acute infection in 60 juvenile diabetic patients were compared with

equivalent data from nondiabetic siblings and from diabetic subjects reported by other workers. While one-third of the diabetic patients had some acute infection other than the common cold within 6 months of the onset of diabetes, the group as a whole was as healthy as nondiabetic siblings except for acidosis and insulin reactions. Limited measurements

**Insulin**—Further evidence that zinc crystalline insulin and amorphous (regular) insulin have a similar effect upon the blood sugar of diabetics has been demonstrated by Jackson, Boyd and Smith<sup>22</sup>. Originally it was claimed that zinc crystalline insulin had an effect upon the blood sugar somewhat intermediate between that of protamine-zinc insulin

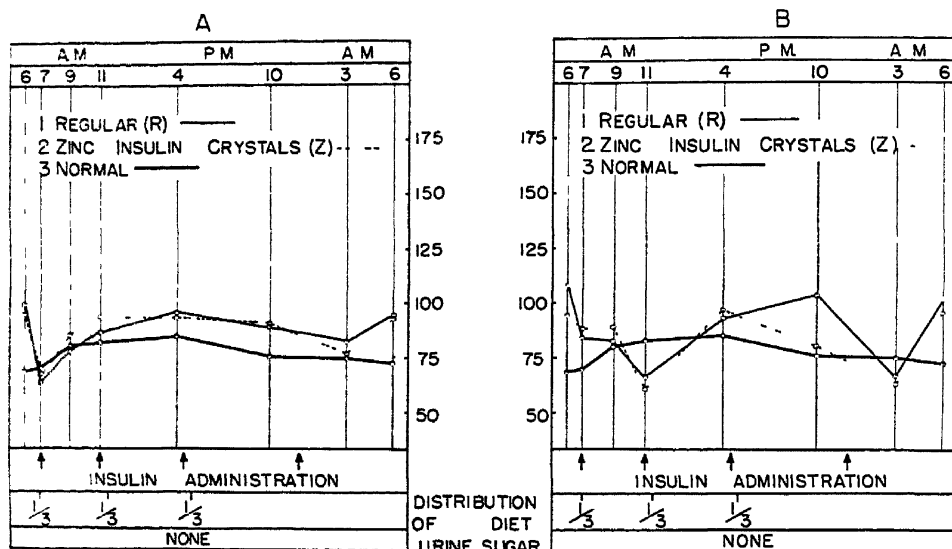


CHART I—Average diurnal blood sugar fluctuations of well stabilized diabetic children receiving equivalent units of amorphous insulin (R) and the zinc crystalline insulin (Z), other factors being constant. In each instance the regimen and response had been constant for several days before blood sugar values were accepted for inclusion (based on an aggregate of 207 hospital days and 336 determinations of blood sugar). The heavy line in each chart indicates average blood sugar values obtained in observations on nondiabetic children under similar dietary regimen. The charts show the values obtained in observations. A, on 6 diabetic children given Lilly's amorphous (R) as compared with Lilly's crystalline (Z) insulin; B, on 8 diabetic children given Stearns' amorphous (R) as compared with Stearns' crystalline insulin (Z). (Jackson, Boyd and Smith. *Am J Dis Child.*)

of this group of juvenile diabetic patients revealed no consistent peculiar deviations from the average in height. The diabetic children were significantly underweight only during the first 6 months of their disease. In contrast to the superior intelligence shown by Joslin's diabetic children, the intelligence of this group showed no deviation from the average and no significant deviation from that of their nondiabetic siblings or from that of the average of Minneapolis children. No characteristic abnormalities in personality were discovered.

and regular insulin in that the effect was manifested later than with regular insulin but earlier than after injection of protamine insulin and that the hypoglycemic effect was longer than with regular, but shorter than with protamine insulin. Clinical observations have not supported this contention. Data from several clinics, among them Mayo's, Joslin's, and that of the reviewer, demonstrated that the effects of crystalline and amorphous insulin upon the blood sugar were essentially the same. The comparable effects of regular and crystalline



insulin as observed by Jackson and his coworkers are shown in Chart I. On the basis of this evidence, these authors conclude that no distinction need be made between the qualitative or quantitative effects of doses of equal unitage of zinc crystalline insulin and of amorphous insulin, or between the effects of corresponding products of various manufacturers.

**Treatment**—Shortly after the isolation of insulin, it was observed that completely depancreatized dogs could not be maintained alive for long, even though adequately treated with insulin. After death the most obvious change observed was an extensive fatty infiltration and degeneration of the liver. It was found then that the addition of raw pancreas to the diet tended to prevent the development of these changes in the liver and to permit survival of the depancreatized dog for longer periods of time. In 1936, L. R. Dragstedt and his coworkers presented evidence indicating that this effect of pancreas was due to a previously undescribed internal secretion manufactured by this gland and effective on oral administration. They suggested the name *lipocaic* for this substance.

Recently Dragstedt<sup>23</sup> has summarized their experience with lipocaic. The assumption that it is an internal secretion of the pancreas is based on the observation that the depancreatized dog, fed on a mixed diet of protein, carbohydrate and fat, is not restored to a normal state by the adequate administration of insulin and pancreatic juice and that the remaining deficiency is corrected by the oral administration of the pancreas but not by other organs. Extracts of pancreas have been prepared which are effective with oral and subcutaneous administration in daily doses of from 60 to 100 mg. of dried substance. Since

these extracts are practically free from lecithin and choline, the former conclusion is confirmed that the beneficial effect of feeding of pancreas in depancreatized dogs cannot be accounted for on the basis of these chemicals.

Two types of *fatty infiltration of the liver* are described in both diabetes mellitus and pancreatic diabetes. *One type* is due to poor control of the diabetes by inadequate administration of insulin and is characterized by a normal or high concentration of the blood lipids and acidosis and is relieved by adequate insulin therapy. The second type is said to be due to lipocaic deficiency and is characterized by a low concentration of the blood lipids, impaired liver function, decreased dextrose excretion, and insulin sensitivity, and is relieved by *lipocaic therapy* but not by insulin. The occurrence of arteriosclerosis in depancreatized dogs is of greater incidence than normal for this species. Dragstedt suggests the possibility of a relation between lipocaic deficiency and this complication both in pancreatic diabetes and in diabetes mellitus.

### Nondiabetic Glycosuria

Bayer and Davis<sup>24</sup> have observed 9 children with what was considered nondiabetic glycosuria for a period of from 2 to 11 years. So far none of them has developed diabetes mellitus. On the basis of their experience, the authors believe that an optimistic outlook may be adopted with regard to the prognosis of children with atypical glycosuria. On re-check, 6 of these children had normal glucose tolerance tests and no glycosuria, 2 had unclassified glycosuria with normal glucose tolerance tests, and 1 had hyperglycemia after ingestion of dextrose together with a decreased dextrose tolerance test.

### Newborn Infants of Diabetic Mothers

Miller and Ross<sup>25</sup> suggest that the hypoglycemia of newborn infants whose mothers have diabetes mellitus may not be the cause of such symptoms as cyanosis, muscular twitching, and convulsions which are frequently found in such infants. The authors have observed 6 infants born of mothers with diabetes mellitus. All 6 of the infants had low concentrations of blood sugar during the first 1 or 2 days of life. In 3 infants abnormal symptoms and findings were

present. In none of these 3 infants was the administration of glucose effective in relieving the symptoms. More striking than the lack of response to glucose was the fact that in each of these infants evidence of organic disease was found which explained more adequately the symptoms and clinical course than did the hypoglycemia. Acute congestive heart disease occurred in 2 infants; both recovered. It was thought that the third infant may have had erythroblastosis fetalis and probably a cerebral birth injury.

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## DIGESTIVE SYSTEM

By WALDO E. NELSON, M.D.

### Stomatitis

**Treatment**—Smith and Johnson<sup>26</sup> state that *chromic acid* (5 to 7 per cent solution) is the only local application which, in their experience, has been efficient in treating acute stomatitis. If the solution is used with the proper technic, improvement begins promptly and the duration of the disease is definitely shortened, especially when treatment is begun early. The relief from pain on eating which follows treatment is sufficient to justify its use. There is no danger of a caustic effect nor of gum atrophy. This solution is also beneficial in relieving the pain and in shortening the duration of the common canker sore.

The technic recommended is as follows: (1) The patient rinses the mouth with a mouth-wash if he is old enough to do so. If there is accumulation of sordes or sloughing material on the ulcerated area, a weak *peroxide solution* is used, followed by a *mouth-wash*. (2) Several swabs of cotton tightly wound on wood applicators are prepared. These swabs should be about the diameter of a lead

pencil and 1½ inches long. The gums and ulcers are dried carefully with a swab. Another swab then is dipped into the chromic solution and applied directly to the ulcers and inflamed edges of the gums. The swab must be wet but not dripping. Some of the solution is gently worked in between the gums and the teeth. It is advisable to dry and treat a small area at a time, not more than one-half to one-third of the dental arch at each operation. (3) Between treatments the patient may use a mouth-wash. (4) The general treatment is that of any febrile illness. *Bed rest* should be continued until the child is able to return to a full diet, not merely during the febrile stage. The authors advise against the use of intravenous salvarsan.

### Diarrhea

**Etiology**—That the dysentery bacillus may be the cause of acute diarrhea in infants and children more frequently than is generally recognized is illustrated by the observations of Cooper, Furcolow, Mitchell, and Cullen.<sup>27</sup> The stools of

209 infants and children suffering from acute diarrhea during the summer of 1938 were carefully studied. Dysentery organisms were recovered from 102 patients (49 per cent). Seasonal incidence, case fatality rate, and duration of gastroenteritis were not significantly different in the dysentery and nondysentery groups. The frequency distribution of the 2 groups, according to the age of the patient, was strikingly different. Seventy-five per cent of the patients under 1 year of age did not have dysentery, whereas it occurred in 75 per cent of those over 1 year. Analysis of the data from the standpoint of the efficiency of the various culture media employed indicated that *sodium desoxycholate citrate medium* was markedly superior for isolating dysentery organisms.

**Treatment** — Further evidence that *banana* and *banana powder* are well tolerated by infants and children with diarrhea is supplied by Wolman and Roddy.<sup>28</sup> Their observations extended over a period of 2 years in which mashed banana or banana powder was employed as the principal food for 97 infants and children with diarrhea. The results were compared with a control group of 80 patients who received a variety of other recognized forms of therapy. The 2 groups were comparable in regard to age, etiologic factors, severity of infection, state of nutrition and mortality rates. In addition to the feeding of banana or banana powder, *parenteral fluids, blood transfusions* and *continuous venoclysis* were administered whenever indicated. The infants and children who received banana were usually relieved of hunger, tenesmus, and abdominal discomfort and passed semiformal stools. The authors conclude that banana diet may be considered a rational addition to the therapeutic management of diarrhea.

### Pyloric Stenosis

**Treatment**—It has been common practice for many years to institute oral administration of fluid and food after *pylorotomy* for pyloric stenosis in infants much earlier than after laparotomy for other diseases. Apparently it has been assumed that the temporary inhibition of peristalsis is not as marked after pylorotomy as after other abdominal operations. Postoperative vomiting after pylorotomy has been of frequent occurrence. Faber and Davis<sup>29</sup> have made roentgenologic studies to determine the degree of *gastric peristalsis* and the *rate of gastric emptying* after the classical Fredet-Rammstedt operation. They found that after pylorotomy for hypertrophic pyloric stenosis there is a profound and prolonged depression of gastric peristalsis which regularly lasts for about 24 hours and may last 3 or 4 days. In the average instance, evacuation of material ingested soon after operation does not begin for more than 8 hours and is not complete until 24 hours after operation. They believe that this depression of peristalsis is closely related to postoperative vomiting which is common and often persistent for several days after the Fredet-Rammstedt operation. For these reasons they have adopted the policy of withholding both water and food for about 24 hours after operation; fluid is administered parenterally during that period and usually also on the next day when oral feeding is started with less than average amounts. The quantity of these feedings is then rapidly increased if there is no vomiting.

Wallgren<sup>30</sup> advises the lingual application of *eumydrine* in the treatment of congenital pyloric stenosis. In 1925, Lindberg called attention to the fact that an alcoholic solution of *atropine* kept its strength and was much more durable

than an aqueous solution and that this preparation could be given satisfactorily perlingually. When eumydrine was introduced, Wallgren abandoned atropine and applied the less toxic eumydrine in the manner described by Lindberg. A 0.6 per cent alcoholic solution of eumydrine containing approximately  $\frac{1}{600}$  gram (0.1 mg.) in each drop was employed. A drop of this solution placed on the surface of the tongue is rapidly absorbed, and the treatment and absorption are not interfered with by the vomiting. The doses employed at Wallgren's clinic have been small in comparison with the amount of eumydrine given orally in aqueous solution. He advises an initial dose of 1 to 2 drops daily, gradually increasing the dose if necessary until the vomiting becomes less severe. The earliest sign of toxic effect is flushing of the face; if this sign appears, the dose is decreased. Usually the vomiting stops or diminishes in intensity before any toxic symptoms develop. He has seldom found it necessary to exceed  $\frac{1}{200}$  to  $\frac{1}{120}$  grain (0.3 to 0.5 mg.) of eumydrine daily.

### Celiac Disease

According to B. B. Breese, Jr., and A. B. McCoord,<sup>31</sup> patients with celiac disease do not absorb vitamin A as efficiently as do children with other diseases. This decreased ability of the patient with celiac disease to absorb vitamin A is usually associated with a flat sugar tolerance curve, increased per cent of fat in the stools, and low carotinoid pigment in the blood. While the inability to absorb vitamin A normally is characteristic of celiac disease, it does occur in other diseases and is, therefore, not pathognomonic of celiac disease. In the authors' cases, even after treatment the ability to absorb vitamin A was still markedly under that of the controls.

### Megacolon

**Treatment**—Good results in the treatment of megacolon with drugs which stimulate parasympathetic action have been reported by Law.<sup>32</sup> He points out that the treatment of this condition may be, in the main, of 2 types, *i.e.*, (a) sympathectomy which blocks out sympathetic inhibitory stimuli to the colon; (b) the administration of a cholinergic drug which stimulates parasympathetic action. The author has employed *acetyl-beta-methylcholine bromide* successfully in the treatment of 6 children with megacolon. In 2 of these cases it was possible to discontinue the drug after 3 and 9 months respectively.

The author's method of management is as follows:

The colon is first emptied by *oil* or *soap-suds enemas* once or twice a day for several days and by the oral administration of from  $\frac{1}{2}$  to 1 ounce (15 to 30 cc) of *liquid petrolatum*. After satisfactory evacuation of the colon, administration of *acetyl-beta-methylcholine bromide* is begun in moderate daily doses and gradually increased up to an optimum effect. In addition,  $\frac{1}{2}$  to 1 ounce (15 to 30 cc) of liquid petrolatum is given each night and enemas are employed when necessary. Usually it requires from 5 to 10 days to strike a balance with acetyl-beta-methylcholine bromide so that there are 1 or 2 stools per day. Enemas may then be discontinued, but it is advised to continue with the liquid petrolatum for several months as a mild mechanical aid. The most effective times for administration of the drug are from  $\frac{1}{2}$  to 1 hour after breakfast and in midafternoon, or at any time to enhance observed daily rhythm of the bowels. If given before breakfast, sweating, nausea, abdominal pain and vomiting are apt to occur. The initial average dose of acetyl-beta-methylcholine bromide is  $1\frac{1}{2}$  grains (0.1 Gm.) administered from  $\frac{1}{2}$  to 1 hour after breakfast, increasing in 2 or 3 days to 3 grains (0.2 Gm.). In another 2 or 3 days it may be increased further, if necessary, by the addition of from  $1\frac{1}{2}$  to 3 grains (0.1 to 0.2 Gm.) given in midafternoon. If this causes diarrhea, the afternoon dose is omitted. After the apparent establishment of a maintenance dose it was sometimes found that the dose

TABLE I  
TYPE AND FREQUENCY OF SYMPTOMS

Symptoms Following Administration	No. of Cases	Percentage
Oral Administration (30 Subjects)		
Nausea	13	43
Vomiting . . . .	7	23
Abdominal pain . .	6	20
(a) in region of umbilicus . .	4	13
(b) in left upper quadrant	1	3
(c) in epigastrium . .	1	3
Constitutional reactions . .	2	7
Oral and pharyngeal symptoms	2	7
No symptoms observed . .	8	27
Rectal Administration (16 Subjects)		
Abdominal pain	12	75
(a) in region of umbilicus	7	43
(b) in upper abdomen	2	12
(c) in left lower quadrant .	1	6
(d) generalized pain.	2	12
Tenesmus . . . . .	4	24
Nausea . . . . .	1	6
Sensation of fullness in abdomen	1	6
Constitutional reaction . . . .	1	6
No symptoms observed . .	3	18

could be reduced from 3 to  $1\frac{1}{2}$  grains (0.2 to 0.1 Gm) administered once per day.

### Acute Abdomen

A series consisting of 58 proved cases of nonspecific *mesenteric lymphadenitis* has been reported by Sobel and Stetten.<sup>33</sup> All but 5 of the patients were under 20 years of age and in 43 per cent of the cases a biopsy of 1 or more lymph-nodes was obtained. It is stated that the dangers inherent in the *removal of a mesenteric node* have been exaggerated. The authors experienced no difficulty nor any untoward effects postoperatively when nodes were removed surgically. In spite of the many theories of the causation of mesenteric lymphadenitis, the exact etiology remains unknown. In the authors' opinion there appears to be some relation to disease of the appendix. Definite adhesions of the appen-

dix were present in 40 per cent of the patients in this series. In 38 per cent of the cases an excess of free peritoneal fluid was found at operation. It is suggested that if, at an operation for acute appendicitis in a child or adolescent, the condition of the appendix does not completely explain the clinical picture, a careful exploration for inflamed mesenteric nodes should be made, especially at the root of the mesentery. They state that at least two-thirds of the patients observed during the first attack of mesenteric lymphadenitis will have future attacks of abdominal pain if operation is withheld. Less than one-third of the patients who had an appendectomy for mesenteric lymphadenitis had attacks of abdominal pain subsequently. The authors point out that, even though there is a suspicion that a given case is one of mesenteric lymphadenitis, opera-

tive interference is indicated because of the danger of neglected appendicitis. Furthermore, they suggest that in some way appendectomy appears to have a relation to the prevention of recurrent attacks of mesenteric adenitis

### Gastroenteric Allergy

Clinical reactions in children with gastroenteric allergy resulting from controlled oral and rectal administration of allergenic foods have been studied by Fries and Zizmor.<sup>34</sup> In view of the controlled conditions in this study, the observations are of particular significance. The clinical manifestations observed are detailed in Table I, and 2 case histories are quoted to illustrate the constitutional type of reaction that simulates an acute abdominal crisis.

#### CONSTITUTIONAL REACTION

"CASE 2—D S, a white male aged 6 years, had been subject to attacks of asthma for the past 2 years. A positive family history of allergy on the maternal side was elicited. Nausea, vomiting, and, occasionally, asthma occurred after the ingestion of egg.

"*Skin Test*—Intracutaneous testing with an extract of egg containing 0001 mg. N per cc resulted in a four-plus reaction.

"*Atopen Used*—Two teaspoonfuls of raw egg in a 6-oz. mixture of barium sulfate in water.

10:00 A. M.: Mixture was swallowed.

10:05 A. M.: Patient complained of a burning sensation in the throat

10:10 A. M.: Sneezing, lacrimation, suffusion of the eyes, and clogged nose were noted. The patient complained of epigastric distress.

10:20 A. M.: Circumoral erythema and swelling of the lips were observed. Numerous small urticarial lesions appeared on the forearm, arms, and neck. There was generalized pruritus.

10:25 A. M.: Patient complained of cramp-like pain in the umbilical region.

10:30 A. M.: The patient was nauseated and vomited a small portion of the test meal.

10:40 A. M. Moderate dyspnea, wheezing, lacrimation, and nasal congestion occurred. The child rubbed his nose and yawned frequently. The ocular conjunctivae were injected. The nasal turbinates appeared pale and swollen. There was a profuse rhinorrhea

10:45 A. M. Patient complained, 'I feel sick,' and held his upper abdomen, complaining of cramp-like pain

11:00 A. M. The itching had subsided, and the urticarial lesions were diminished in number and size. Patient appeared improved.

1:00 to 4:00 P. M.: During this interval, there were 3 watery bowel movements."

#### ACUTE ALLERGIC ABDOMEN

"CASE 5—M. L., a female of allergic lineage, aged 8 years, has been subject to recurring attacks of asthma for 2 years. Until the age of 3 years, the child had vomited following the ingestion of egg. Since then, several trial feedings of egg have been followed by cramp-like abdominal pain, usually within 2 or 3 hours.

"An oral test meal of barium sulfate was not followed by any symptoms. Two weeks later, a similar study was made when half of a raw egg was added to the barium meal.

"*Skin Test*—Intracutaneous tests with an extract of egg (0.1 mg. N per cc.) gave a three-plus reaction.

"*Atopen Used*—One tablespoonful of raw egg in a 6-oz. mixture of barium sulfate and water.

9:50 A. M.: The allergen-containing meal was ingested.

10:00 A. M.: The patient complained of nausea. A small amount of the mixture was vomited. An equivalent amount was fed to the patient.

10:00 to 11:00 A. M.: Patient felt perfectly well during the entire period.

11:10 A. M.: The child was seized with severe cramp-like abdominal pain which prostrated her.

11:20 A. M.: Paroxysms of abdominal pain recurred at 10- to 15-minute intervals. During these paroxysms, lasting 3 to 5 minutes, the child

screamed and doubled up with pain which was localized at a point just above the umbilicus. Deep palpation elicited tenderness in the epigastric region. Neither rigidity of the abdom-

inal wall nor rebound tenderness was present.

12:30 P. M. Patient wheezed moderately.

1:30 P. M. There was an abrupt cessation of pain and patient recovered immediately from her disability"

## DIPHTHERIA

By ROBERT A. LYON, M.D.

**Mortality**—The diphtheria mortality rate in 93 large cities declined during 1939 to 0.82 per 100,000 population (17th Annual Report).<sup>35</sup> The cities of the middle Atlantic seaboard had the lowest rates but a total number of 32 cities in various parts of the country had no deaths from diphtheria during the year. Twenty-two cities of this group have had no diphtheria deaths during 1938 and 1939.

The clinical severity of diphtheria in 7 cities of Great Britain has been surveyed from the records of 1911 to 1935 by H. D. Wright.<sup>36</sup> The case fatality rate was employed as a measure of the severity of diphtheria. While it was not always true that this rate indicated the true nature of the diphtheria epidemic, it was the most accurate group of statistics available. During this period of 24 years, there was a decline in the fatality rate in all of the cities but the declines occurred in different years. In some of the cities there was a tendency towards level and uniform fatality rates while in other cities the extremes were more noticeable. During the years 1931 to 1935 there was a general rise in the fatality rate, although this increase was not always associated with an epidemic of diphtheria. There seemed to be a relationship between the age group involved and the fatality rate. During the period of years, the case fatality rate of children of school age, 5 to 9 years of

age, declined less than that of groups of other ages. The severity of diphtheria throughout the period of investigation seemed to have declined although there were increases in severity in the past few years in the children of the 5- to 9-year group. Causes of these variations were difficult to determine. It may have been that the number of immunized children of preschool age had increased, that general health standards among this age group had been improved, or that variations had occurred in the strains of diphtheria bacillus from the gravis to the intermediate or mitis type.

**Pathology**—The effect of diphtheria toxin upon the cardiac glycogen stores of experimental animals has been investigated by McDonald and DeGroat.<sup>37</sup> Six dogs who received various doses of diphtheria toxin had daily electrocardiograms and determinations of the glycogen distribution in the tissues of the heart. The major changes of the electrocardiograms were various degrees of block, depression and notching of the S-T segments and abnormalities of the T-waves. The pathological changes occurring in the heart muscles consisted of streaks of hyaline, with swelling or shrinking of the nuclei. The glycogen distribution throughout the heart and the total content were not greatly altered by the administration of toxin. A slight rise of about 10 per cent in the glycogen content in the total heart which gener-

ally occurred may have been the result of starvation, rather than of the toxic effects of the diphtheria

In the toxemia of diphtheria, the adrenalin content of the suprarenal glands of experimental animals has been found to be normal by Ashford.<sup>38</sup> Although the effects of toxin varied widely in the different animals, no difference of statistical significance existed between these results and those obtained in normal animals. Little basis could be found for the theory that circulatory collapse in diphtheria patients is due entirely to reductions in adrenalin output of the adrenals. Histologically, the glands showed evidence of hemorrhage, fatty degeneration, and depletion of the chromaffin tissue.

**Diagnosis**—The rapid clinical test for diphtheria by the local application of a 2 per cent aqueous solution of *potassium tellurite* has been evaluated by Fox, Rhoads and Lack.<sup>39</sup> This solution is supposed to turn the diphtheritic exudate a blackish color and not to affect the exudate caused by other organisms. When the solution was applied to the throats of 27 patients, the test was positive in all of the 17 who had positive cultures for the diphtheria bacillus. In the other 10 patients whose cultures were negative for diphtheria but positive for other organisms, such as the streptococcus or Vincent's organisms, the test with the potassium tellurite solution was positive in 1 and negative in the other 9 cases. The authors believe that the test was accurate in a sufficiently high percentage of instances so that it would be safe to withhold specific antidiphtheria treatment from those with negative reactions until a culture could be examined 12 to 18 hours later, while in the patients with positive reactions, treatment could be started immediately.

Further investigation of the *potassium tellurite test* has been carried out by Cooper, Peters, Wiseman, and Davies.<sup>40</sup> In 57 patients with bacteriologic evidence of diphtheria the test failed in 13 instances. In another group of 27 patients with no bacteriologic proof of diphtheria, the test was falsely positive in 15 cases. In another series of experiments, the swabs containing nose and throat secretions were applied to the potassium tellurite plates. Positive results were obtained with 88 per cent of the throat swabs which were bacteriologically positive for the diphtheria bacillus, but only 32 per cent of the positive nasal swabs gave positive tests with the tellurite. Negative nose and throat swabs were positive with tellurite in 34 per cent of cases. The percentage of false reactions with the potassium tellurite seemed too high to make the test practical for general use. The authors suggest that the reaction of darkening of the tellurite solution was not specific for the diphtheria bacilli, but might be due to some reduction system common to many bacterial cultures.

Difficulties encountered with the use of *Loeffler's medium* in making an accurate diagnosis of diphtheria have been mentioned by Perry and Petran.<sup>41</sup> Errors in 50 to 75 per cent of cases have been made with different samples of the medium due to variations of pH, and to technics of preparation. Success was greater with serum tellurite agar plates which allowed for more ready differentiation of diphtheria bacilli from diphtheroids and also permitted the identification of types of *gravis* and *mitis* bacilli with considerable accuracy.

The importance and value of *direct smears* for the rapid identification of diphtheria bacilli has been stressed. More than half of the swabs from diphtheria patients have given positive re-



sults on direct smear and in only 1 instance was a positive smear reported which was not confirmed by culture methods.

**Immunization**—A summary of the recommended procedures for diphtheria immunization has been filed by a Committee on Evaluation of Administrative Practices.<sup>42</sup> It was recommended that:

"1. The preferred practice should be for children under school age, and preferably for those at the ninth month of life, (a) 2 doses of *diphtheria toxoid, alum precipitated*, with a 4-week or 1-month interval between the doses, or (b) 3 doses of diphtheria toxoid at 4-week or 1-month intervals.

"2. In the communities where it is impracticable to give 2 doses of diphtheria toxoid, alum precipitated, or 3 doses of diphtheria toxoid, (1a or b), to all the children between 9 months and 10 years of age, it will probably be found that the giving of 1 dose of diphtheria toxoid, alum precipitated, to a large number of children of this age group is more effective in preventing diphtheria in the community than the use of the 2 or 3 doses (1a or b) for half as many children.

"3. To those children receiving 1 injection of diphtheria toxoid, alum precipitated, a single reinforcing dose of not more than one-half the usual dose of an equivalent diphtheria toxoid, alum precipitated, preparation should be given to each child inoculated in infancy, just prior to the child's entering school at 5 or 6 years of age, or 3 to 5 years after the initial inoculation if this has been carried out at some time later than the first year of life.

"4. As a routine procedure the performance of the Schick test 3 to 6 months after completion of the inoculations in infancy is not considered to be essential, although it may be desirable in private practice and whenever the personnel and condition of access to patients at public clinics makes this additional contact practicable.

"5. (a) Children of 10 years of age or over who are known to be susceptible as the result of the Schick test should receive 3 doses of diphtheria toxoid at 4-week or 1-month intervals, or equivalent doses of toxin-antitoxin similarly spaced. (b) For susceptible adults who may be exposed by occupation to contact with the clinical or carrier stage of diphtheria, the use of diphtheria toxoid, alum precipitated,

is not recommended. In the case of adults with occupational hazards (*e.g.*, physicians, nurses, attendants in hospitals for communicable diseases), those reacting to a sensitivity test should not be inoculated; others should receive 3 doses of diphtheria toxoid or toxin-antitoxin as advised for children over 10 years of age (5a). The routine period of Schick test should be 12 months after completion of inoculation, unless there is a special reason for giving the Schick test earlier. The immunity produced is probably at its highest 3 or 4 months after the completion of the inoculations.

"6 The practice of administering diphtheria toxoid in 2 doses at 3-week intervals should be discontinued."

The importance of giving more than 1 injection of *alum precipitated toxoid* in order to produce prolonged immunity has been emphasized by the observations of Nevius and McGrath.<sup>43</sup> In a series of 72 children, who had negative Schick reactions 1 year after the injection of 1 cc. of alum precipitated toxoid had been administered, only 80 per cent were Schick-negative after a period of 5 years. Of a group of 78 children who received 3 injections of 1 cc. of toxin antitoxin, 96 per cent were negative at the end of a 5-year period. At least 2 injections of 1 cc. each of alum precipitated toxoid should be given at intervals of 2 or 3 weeks. This seemed to be necessary for more permanent immunity, and Schick tests should be performed 1 year, 3 years, and 5 years afterwards. If during this time any reversals of the Schick test from negative to positive had occurred, another cubic centimeter of the toxoid might be given.

The *results* from active immunization against diphtheria in Cincinnati have been reviewed by Harder, Gelperin and Cook.<sup>44</sup> A general decline in the mortality rates from diphtheria in the locality coincided with the campaign of active immunization, although the mortality rates of children who had been inoculated and of children who had not been

inoculated were approximately the same. In a series of 474 untreated diphtheritic patients, 22 deaths had occurred or a mortality rate of 4.6 per cent, while in another group of 238 inoculated patients there had been 11 deaths, about the same fatality rate. The disease had occurred primarily among the lower economic groups. Very little difference of effectiveness could be detected between 3 injections of toxin-antitoxin, plain toxoid, and alum precipitated toxoid, but several injections of any of these materials gave better immunization than the single injection.

In the determination of the *effectiveness of curative and preventive methods* employed to combat a disease such as diphtheria, care must be taken to analyze the natural morbidity and mortality trends of the disease. Seckel<sup>45</sup> has examined the trends of diphtheria morbidity in certain localities of Europe and this country since the latter part of the XIX Century. Before the introduction of preventive measures the waves of incidence rose and fell, with peaks every 8 to 17 years in central Europe. In the United States the peaks of incidence were not as high but occurred about every 6 or 7 years.

Widespread immunization against diphtheria was begun about 20 years ago when a natural decline in the incidence of diphtheria was occurring. In 1927, an increase in the number of diphtheria cases occurred as usual but the concerted drives to immunize children since that time have leveled the expected peaks of 1930 and 1934 to scarcely perceptible levels. In parts of Europe where immunization had not been carried on so extensively, epidemics of the disease have not been prevented. Diphtheria among immunized patients has been much less severe than in unimmunized groups. The importance of employing

control groups in studies of the efficacy of immunization procedures has been stressed by the author, unless long periods of time are included to allow for natural waves of increased or decreased incidence of the disease.

**Combined Diphtheria and Tetanus Immunization**—The results of combined active and passive treatment of diphtheria and tetanus have been reviewed by Ramon.<sup>46</sup> In his experience the immediate injection of antitoxin in either of these diseases, followed by the repeated injections of toxoid material, has resulted in the immediate building up of the antitoxin protective bodies in the individual afflicted with the disease. This has not interfered with the effectiveness of later injections of the antigen in stimulating a permanent, active immunity of the individual. During the period of convalescence the antitoxin levels in most patients remained sufficiently high to protect the patients against recurrent attacks of the infection.

**Tetanus Toxoid Reactions**—Reactions following the injection of tetanus toxoid in adults have been recorded by Whittingham.<sup>47</sup> In a series of more than 61,000 individuals, local reactions occurred in about 1 per cent, and constitutional symptoms of headache, slight degrees of fever, or urticaria occurred in 0.02 per cent. Severe anaphylactic shock occurred in 2 patients. Another instance of anaphylaxis following the injection of tetanus toxoid has been reported by Parish and Oakley.<sup>48</sup> The necessity of having at hand *adrenalin* for combating such severe cases of anaphylaxis was recommended in both reports.

Allergy induced by the injection of tetanus toxoid has been reported by Cooke, Hampton, Sherman, and Stull.<sup>49</sup> Several instances of urticarial reactions and 1 case of rather severe sensitizations

have occurred in the patients observed by the authors. The reaction usually occurred at the time of the injection of the second dose. In order to avoid such reactions they recommended that a *scratch epidermal test* be employed to detect the sensitivity of the patient. If the patient is sensitive, small injections of 0.2 cc. of a 1-10 dilution of the toxoid are started and the dosage is gradually increased if reactions are not severe. The importance of having *adrenalin* handy is emphasized and the use of a *tourniquet* above the site of injection is sometimes valuable in delaying the absorption of the material until adrenalin can be injected. It is suggested that some culture media for the tetanus bacillus which contained less antigenic material such as proteose might be employed in the production of the tetanus toxin.

**Schick Reaction**—The sensitivity of the skin to the Schick reaction was not affected by another disease such as scarlet fever in the investigation carried out by Duffy and Mitchell.<sup>50</sup> In a series of 22 patients with scarlet fever varying in age from 2 to 13 years, 8 were positive to the Schick reaction and all of these had less than 0.002 unit of diphtheria antitoxin per cubic centimeter of serum. The remaining number of children had negative Schick reactions and all except 2 had more than that number of units of antitoxin. Scarlet fever did not influence the normal response of the skin to the diphtheria toxin, since the correlation between the antitoxin content of the blood and the reaction of the skin to the injections was very close.

The *reversal* of negative Schick reactions to positive ones in a group of children observed by Hillman and Linde<sup>51</sup> was 25.5 per cent during a period of 2 to 4 years. These children had received 2 doses of unmodified toxoid. This indicated the necessity of re-testing children

at the time of entering school. It has become customary to give infants their initial injection of toxoid during the second 6 months of life. The authors have noted in their series that a higher percentage of infants became Schick-negative when immunization was started at the age of 6 months rather than at 1 year of age. The practice of Schick-testing infants 6 months after the completion of their immunization was shown to yield a high percentage of negative reactions but at the end of 1 year the reversion from negative to positive began. Three doses of ordinary toxoid administered at intervals of 1 month seemed to be more effective as an immunizing agent than 2 injections of the material. Males developed negative Schick reactions in greater percentages than did females receiving the same dosage.

The incidence of *spontaneous changes* in the Schick reaction has been reported by Lyon and Mitchell.<sup>52</sup> A series of 453 children of school age residing in an institution were given repeated Schick tests over a period of 5 years. From 4 to 16 per cent of the children who had been negative at the first test reverted to positive from year to year. This high degree of fluctuation of antibody levels would lead one to doubt the immune status of any individual over a period of time. In order to avoid any false sense of security from a previous Schick reaction, the authors recommend the plan of giving a protective dose of the immunizing agent to a child every 2 or 3 years to raise the antitoxin titers to high levels so that later fluctuations will not reduce his protective powers to dangerously small amounts.

The *immunity* of children who have had attacks of diphtheria has been compared with the immunity of those children who had been actively immunized by Warin.<sup>53</sup> A group of 110 children

who had been artificially immunized between the years 1930 and 1935 received the Schick test and all but 7 per cent were negative. In another group of 92 children who had suffered from attacks of diphtheria during the same period of time all but 25 per cent were negative. It was questionable whether the immunity received by the diphtheria infection might not have been a somewhat different type from that received by the injections, or that the Schick reaction may not have been an accurate measure of the protection. It was also possible that a primary attack of diph-

theria may not have conferred complete immunity to an individual and very mild subclinical attacks may have occurred in subsequent years.

A *new Schick toxin* has been devised by Taylor and Moloney<sup>54</sup> which permits of more distinct readings and is more stable to heat. A toxin of double toxicity was employed in conjunction with standard toxin in testing a group of patients with  $\frac{1}{200}$  or more of antitoxin in their blood serum. Reactions of a definite nature capable of accurate interpretation were obtained more frequently with the new toxin.

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## ENDOCRINE DISTURBANCES

By JOSEF WARKANY, M.D.

### Obesity in Children

Bruch<sup>55</sup> discusses some aspects of *physical growth and development* of obese children. Fifty-one boys and 51 girls were studied and it was found that these children showed a growth in stature in excess of the average, a finding reported previously by Czerny and Keller and others. Skeletal maturation was found to be normal or advanced and the sexual maturation was not delayed. The majority of the boys between 11 and 14 years of age showed signs of maturation and the author denies that obesity is a concomitant manifestation of hypogenitalism. The age of menarche of obese girls was found below the lower limit of the normal range. A similarity thus exists between the growth pattern of obese children and normal (nonobese) children who mature early. This type of obesity found in children before the age of puberty should not be considered as hypothyroidism or hypopituitarism. This is also brought out by another study by the same author<sup>56</sup> concerning

the *basal metabolism* and *serum cholesterol values* observed in obese children. It is pointed out that determinations of the basal metabolism as ordinarily carried out do not represent a basis for the estimation of the part played by the thyroid in the pathogenesis of obesity. The lack of relation between the serum cholesterol concentration and the basal metabolic rate speaks against the assumption that hypothyroidism plays an important rôle in the pathogenesis of simple obesity. The fact that these laboratory methods do not explain the nature of the disturbance in obesity, however, does not exclude the possibility that the endocrine balance or the intermediary metabolism of obese children are abnormal.

Talbot and Worcester<sup>57</sup> report their work on the relationship between *basal energy metabolism* and the active protoplasmic mass as measured by creatinine. The studies begun with normal children were extended to obese children. The results show that the basal metabolic

rate of the protoplasmic mass is moderately elevated in obese children. This indicates that such children do not necessarily suffer from a deficiency of anterior pituitary or thyroid hormones.

A series of children presenting the *adiposogenital syndrome* were studied by Schwarz, Newman and Baum<sup>58</sup> with regard to their reaction to several biological tests and the concentration of fat metabolism hormone in their blood. It was assumed that the ability of the human serum to increase the ketone concentration of the blood of the rat can be used as an index of the concentration of circulating fat metabolism hormone. The blood in cases of adiposogenital dystrophy caused an increase of 7 per cent of the blood ketones of male rats, while no significant changes were produced by the blood of normal children. This finding could be interpreted to indicate that in adiposogenital dystrophy a tendency is present for a higher concentration of fat metabolism hormone. The insulin sensitivity test did not reveal an essential difference between cases of adiposogenital dystrophy and normal children. The gonadotrophic principle could not be demonstrated in the blood of normal children nor that of children with adiposogenital dystrophy. Administration of anterior pituitary-like gonadotrophic hormone produced gonadal development without affecting the obesity of the children.

### Exophthalmic Goiter

**Results of Treatment**—The late results of surgical and medical treatment of exophthalmic goiter in children were studied by Kennedy.<sup>59</sup> Of 163 children, 138 had been treated surgically and 25 medically. The results of *operation* were entirely satisfactory in 106 patients; fair in 23, and in 1 case they were poor. Recurrences occurred in 12 patients. Low

basal metabolic rate or myxedema followed operation in 19 cases. In respect to *medical treatment* it was found that operation had become necessary in a number of patients at a later date but that in mild cases a normal adult status could be attained by restriction of activity and the administration of compound solution of *iodine*.

### Neoplasms in Pathogenesis of Endocrine Disorders

A study of neoplasms producing endocrine disturbances in childhood was published by Gross.<sup>60</sup> *Granulosa-cell carcinoma of the ovaries* cause the following triad of symptoms: (1) an enlarging mass in the lower part of the abdomen or the pelvis; (2) hypertrophy of the breasts, nipples or labia; (3) discharge of blood from the vagina. Estimations of 24-hour specimens of urine show an enormously increased output of estrogen.

The *symptoms* of a neoplasm of the *adrenal cortex* in a girl consist of enlargement of the clitoris, appearance of pubic hair, and development of masculine body build, of a husky voice, of acne, and of precocious ossification. In the male the same extragenital symptoms are combined with precocious development of the penis and testicles. Neoplasms of the *adrenal medulla* may cause crises of hypertension. They are rarely seen in children.

*Pineal neoplasms* causing precocious puberty have been observed in boys only. Advanced somatic growth, moderate adiposity, and mental precocity are usually part of the syndrome. Signs of increased intracranial pressure and involvement of the corpora quadrigemina accompany the endocrine symptoms.

*Tumors of the floor of the third ventricle* may cause endocrine symptoms in

girls as well as in boys: Precocious maturation of the genitalia corresponding to the sex of the child, appearance of secondary sex characteristics, excessive somatic development, advancement in the bone age, and sometimes disturbance of the water balance have been observed in such cases. It is important to note that these endocrine signs are not necessarily associated with symptoms of an expanding intracranial lesion.

### Cryptorchidism

**Treatment**—Zelson and Steinitz<sup>61</sup> report the results of treatment of cryptorchidism with *male sex hormone*. It

seems that *gonadotrophic hormone* is more effective than male sex hormone in the treatment of cryptorchidism. The results obtained with *testosterone propionate*, however, are certainly of theoretical interest. Of 20 boys treated with this hormone, 17 had unilateral and 3 bilateral undescended testes. Only 3 of these cases responded to treatment with testosterone with complete descent of the testes, while 9 showed a partial effect. It was observed that male sex hormone will produce an enlargement of the penis and scrotum and growth of pubic hair, but has a tendency to cause a shrinkage in the size of the testicle.

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## FEEBLEMINDEDNESS IN CHILDREN

By ROBERT A. LYON, M.D.

**Normal Variations of Intelligence Quotients**—The normal variation of the intelligence quotients in children living under constant environments has been stressed by Strauss and Kephart.<sup>62</sup> Of a large group of patients in institutions, repeated intelligence tests of 41 per cent increased 4 to 5 points over a period of time, 33 remained constant, and 26 per cent decreased. The author emphasized the importance of considering the spontaneous variability of the intelligence quotients which may occur in any group observed over a long period of time.

**Etiology**—*Fetal or neonatal asphyxia* has been described as a possible cause of mental deficiency by Schreiber.<sup>63</sup> The lack of oxygen supplied to the brain during fetal life, during delivery, or immediately afterwards may cause a permanent damage to the nerve cells. Several pathologic sections of the brains of infants dying at birth or soon after were described in which there were areas of

necrosis and deterioration without any evidence of hemorrhage or other gross defects. These infants had histories of prolonged delivery and their mothers had had considerable anesthesia. Four different types of conditions which would lead to an inadequate supply of blood to the brain were described. First, the *anoxic type*, due to some mechanical obstruction to the infant's breathing or to the result of a prolonged anesthesia of the mother with a substance like nitrous oxide, or finally to some other maternal condition, such as pneumonia or strangulation, which might reduce the oxygen supply. The second type was the *anemic type*, in which the mother suffered from a marked reduction of red cells throughout pregnancy. The third was the *stagnant type*, in which the heart or blood-vessels in some manner reduced the supply of oxygen to the brain of the mother and to the fetus throughout pregnancy. In this category might be placed the prolonged use of sulfanila-

mide, which would have some influence in diminishing the available oxygen supply of the mother for long periods of time. The final type was designated as a *histotoxic type*, in which the cells of the body were so damaged that oxygen could not be utilized adequately. The extensive use of drugs such as morphine and some of the barbiturates might cause such a condition. The author concluded that it was of importance to examine the birth histories of mentally defective infants and children to determine whether or not there might have been some relationship between the mental condition and anoxemia.

In a review of the incidence of *syphilis* among the feeble-minded, made by Hays,<sup>64</sup> about 4.8 per cent of large groups of patients in asylums had evidence of syphilis as compared with 8 per cent of pregnant women and 9.5

per cent of hospital and dispensary patients. This low incidence of the disease among the feeble-minded may be the result of high death rates among congenital syphilitics or the failure of detection of some of the syphilitics because of inadequate examination, especially of their cerebrospinal fluids.

**Treatment**—*Thiamin chloride* has been administered to patients with mental deficiency by Lewald and Alexander.<sup>65</sup> It had been hoped that this vitamin which is beneficial in the treatment of polyneuritis might be of some value in the treatment of mental defectives. The vitamin was given in large doses to a group of 8 mental defectives varying in age from 3 to 10 years. No significant changes in their mental condition were noted but the children seemed to show some improvement of their physical status

## GENITOURINARY SYSTEM

By WALDO E. NELSON, M.D.

### Urine Collector

A device for the collection of urine in infants, especially females, which eliminates the need for adhesive tape, has been devised by Cohen and Blatt.<sup>66</sup> This collector has been found to be efficient for use in the home and office as well as in the hospital.

The collector and its application are illustrated in Figs. 1, 2 and 3. The collector is a single unit constructed of rubber. It has a large recess which gradually narrows to form a funnel-like spout. The recess lies next to the vulva when the device is applied. The spout protrudes about 2 inches and has a standard test-tube inserted into it to serve as a receptacle for the collected urine. On the inner aspect is a rubber

trough,  $\frac{1}{8}$  inch thick, which acts as a partition at the perineal area. Attached to it at its midportion is a rubber perineal button. The partition keeps the

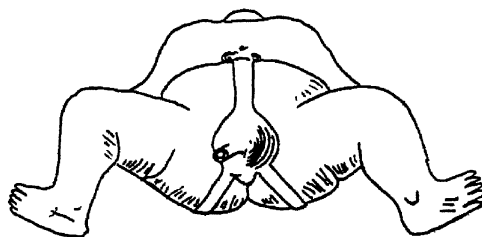


Fig 1—View prior to placing the test tube in rubber spout. (Cohen and Blatt: *Am. J. Dis. Child*)

sprayed urine from dribbling into the rectum and aids in directing it into the recess. The button and the partition also keep any feces that may be passed from working into the recess and thus

prevents contamination. The collector has 3 flat rubber supports with safety pins at their ends for attachment to the infant's undergarments

The *advantages* claimed for this device are: (1) It is a simple unit; (2) it can be sterilized, (3) it is easily applied by a physician, nurse, or layman; (4) since it is composed of soft rubber it causes

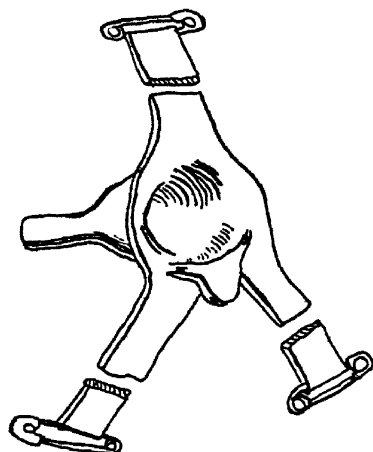


Fig 2 — Posterior view, showing recess, partition combined with perineal button, and safety-pin fasteners (Cohen and Blatt: *Am J Dis Child.*)

no irritation or trauma about the genitalia; (5) it can be left on a considerable length of time; (6) it eliminates the necessity of using adhesive tape; (7) it may be employed for both male and female infants.

### Bladder Training

Observations relative to the optimum time to introduce *toilet training* in infants have been made by McGraw.<sup>67</sup> Two sets of identical twin boys were under intensive study during 17 and 28 months, respectively, for the purpose of determining basic behavior changes accompanying voluntary control of micturition. One member of each pair of twins, after the first month of life, was subjected to a program of being placed on the chamber at hourly intervals during 7 hours of the day. Their twins were

not allowed on the chamber until they were 14 and 24 months of age, respectively, at which time they were exposed to the same schedule of toilet training. In both instances the achievement of these boys approximated that of their brothers, even at the onset of their training schedule. It is suggested that toilet training be delayed until the child's general behavior indicates cortical participation in the act of micturition.

### Nephrosis

**Treatment**—Further observations on the use of *concentrated human blood serum* as a diuretic in nephrosis have been made by Aldrich and Boyle.<sup>68</sup> Seven additional patients, with a diagnosis of what the authors term pure nephrosis, were treated with 4 times concentrated pooled human serum. Diuresis usually occurred in these patients, and as a rule there was complete elimination of edema fluid, and apparently in some instances there was complete recovery from the nephrosis. Patients with other types of renal edema, notably those associated with hematuria, were not benefited. On the basis of their experience, the authors believe that much better results can be expected from this treatment if it is employed early in the course of the disease rather than later. They also suggest that concentrated serum may be ineffective when administered in the presence of an acute infection. Reactions to the concentrated serum were insignificant unless hemolysis had occurred in the serum. The serum should be distinctly yellow and not red.

### Undescended Testes

**Treatment**—In view of the current enthusiasm for *hormonal treatment* of undescended testes, it appears in order to mention the conservative management advocated by R. E. Smith.<sup>69</sup> In his ex-



perience, spontaneous descent occurred at about the time of puberty in a high proportion of cases. He states that spontaneous descent rarely occurs when there is an associated hernia. It is his opinion that there is no harm in postponing operation or gonadotrophic hormone therapy until puberty, at which time

*picrate suppositories* is recommended by Holmes, Jones, and Gildersleeve.<sup>70</sup> Each suppository contained 1 grain (0.065 Gm.) of silver picrate, which was approximately equivalent in silver content to 16 minims (1 cc.) of a 10 per cent solution of mild silver protenate or to  $\frac{3}{4}$  dram (3 cc.) of a 1 per cent solution

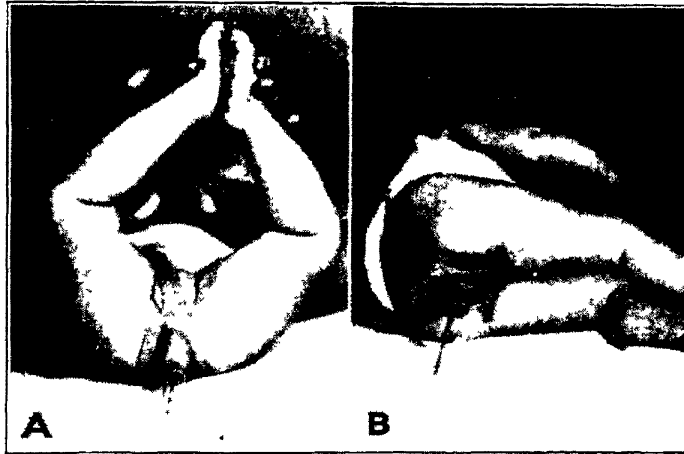


Fig. 3—Urine collector in place. *A*, caudad view. *B*, posterior, showing that change in position does not affect collector. (Cohen and Blatt. *Am J. Dis. Child*)

there is possibly an access of gonadotrophic hormone into the circulation. Grave coincident disorders, such as torsion, tumor, or inflammation, were not noted. The testes which descended spontaneously at the time of puberty were apparently functionally perfect.

#### Gonorrheal Vaginitis

**Treatment**—Treatment of gonorrheal vulvovaginitis in children with *silver*

of silver nitrate. A suppository was inserted into the vagina by the mother each evening except that preceding the weekly visit to the clinic. In most instances there was cessation of profuse discharge and disappearance of gonococci from vaginal smears in 1 to 2 weeks. The average time required for cessation of symptoms was 3.2 weeks. Six of 20 cases, followed at least 6 months, were listed as recurrent.

## GERMAN MEASLES (RUBELLA)

By ROBERT A. LYON, M.D.

**Symptoms and Complications**—The severity of rubella when it occurs in epidemic form has been illustrated in the report of Bennett and Copeman.<sup>71</sup> An outbreak of the disease affecting more than 300 patients occurred in Brit-

ish military hospitals during the months of February and March, 1940. The symptoms of the disease which increased in severity as the epidemic proceeded, consisted of swelling of the mucous membranes of the nose, palate and

gums; high fever and, occasionally, stiff neck and occipital headache. Among the interesting complications were those of muscle and joint pains, which occurred with considerable frequency. Generally, the pains developed on the third day of the disease, although in some cases they were not noticed until the ninth day. Usually the pains were gone by the time that the rash disappeared, but in some cases the joint involvement was so severe that it resembled rheumatic arthritis, and occasionally fluid accumulated in the joints and

cardiac complications were noted. Sore throat with a yellowish patchy exudate suggesting follicular tonsillitis occurred in a large number of patients towards the latter part of the epidemic. The gums, also, tended to become swollen and tender, so that the symptom of toothache was common. Relapses of the disease occurred in 8 per cent and secondary rises in fever in about 10 per cent of the group. Leukopenia was noted in the majority of the patients, and lymphocytes were the predominant cells present.

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## HEART DISEASE IN CHILDREN

By ROBERT A. LYON, M.D.

### Congenital Heart Disease

**Diagnosis**—The characteristics of various types of congenital heart disease observed in 32 infants have been reviewed by Ash, Wolman and Bromer.<sup>72</sup> Of this group, the correct diagnosis had been made previous to death in 14 or 43.7 per cent. In 3 instances, congenital heart disease was not suspected and in the others some cardiac disorder was suspected but not accurately diagnosed.

In a group of patients with possibilities for the shunting of arterial blood to the venous side of the heart (*cyanose tardive*) no cyanosis developed except terminally, in association with pneumonia, in 92 per cent of cases. On the other hand, the absence of cyanosis did not always indicate the absence of a lesion which would permit shunting of venous blood into the arterial circulation. Six of a group of 16 infants with lesions permitting venous arterial shunt had no evidence of cyanosis during the first month of life.

Polycythemia often preceded the occurrence of cyanosis but the blood count

was sometimes influenced by other factors. Dehydration of the infant tended to raise the red cell count and infection or malnutrition caused a decrease.

Murmurs often helped to make a *diagnosis* but were occasionally absent entirely, especially in the first few weeks and in terminal stages of a patient's life. *Electrocardiograms* were of assistance in making the diagnosis of dextrocardia and certain arrhythmias such as heart block. Right axis deviation of various degrees accompanied lesions of the pulmonary artery and the absence of this form of axis shift indicated hypertrophy of the left ventricle which might accompany aortic stenosis or coarctation of the aorta. Occasionally no axis shift was noted in cases of marked hypertrophy of one or other of the ventricles.

*Roentgenograms* were of considerable help in the determination of the size of the various portions of the heart. When the shadows of the ventricular area of the heart were enlarged, it was often impossible to tell whether the right or the left ventricle was responsible for

the increase in size. In young infants with congenital cardiac defects, the roentgenograms did not always show the enlargement which might be expected.

*Lactic acid levels* in the blood stream of patients with cyanotic types of congenital heart disease have been shown to increase after exercise. Hallock<sup>73</sup> found that such patients had normal amounts during rest, but after exertion the levels were consistently higher than in those patients with acyanotic types of congenital cardiac defects. Tissue anoxemia therefore did not seem to be present in the cyanotic patients at rest but was potentially present, as manifested by the rapid development of the acid, after exercise. The degree of cyanosis did not always indicate the amount of the deficiency of oxygen. In 1 patient, deeply cyanotic, the levels of lactic acid did not rise with exercise. From these tests and from those of patients with various types of acquired heart disease, the author concluded that blood lactate levels were influenced by either the shunting of venous blood into the arterial circulation or by myocardial insufficiency rather than by any other specific valvular or anatomic defects of the heart.

**Prognosis**—The prognosis of congenital heart disease in children has been reviewed by R. Ash and E. Harshaw, Jr.<sup>74</sup> The records of 230 children with congenital heart disease observed during the years 1922 to 1936 were reviewed, and information regarding the course of 80 per cent of this group was obtained. Several more of the group had been followed for shorter periods of time, so that a total of 94 per cent had been observed for 2 years or more. Death occurred in 102, and the majority of these were children less than a year of age. This group constituted 73 per cent of the deaths. Of the 94 children of school age when first seen,

11 per cent had died. The cause of death in slightly more than half of the patients was due to some infection, usually pneumonia. Bacterial endocarditis had occurred in only 2 instances. Sudden death had occurred in 1 child with heart block and in another with aortic stenosis following slight traumatic injuries over the chest. The death rate of the infants who were cyanotic was about twice as great as that of the noncyanotic group. Eighty per cent of the school children who were cyanotic were dead by the end of the period of observation, while only 5 per cent of the noncyanotic children had died. Only an occasional instance of a cyanotic patient living to young adulthood was recorded. A marked degree of polycythemia in itself did not seem to be any deterrent to longer life. Mental retardation was noted in 34 children, or 14.5 per cent of the group, but it was questionable whether the cardiac lesions had had any influence on the cerebral circulation which might have caused the mental disturbances. Among the feeble-minded group were 3 Mongolian idiots and 1 microcephalic idiot, whose defects were independent of cardiac disease. Malnutrition, which was observed in 30 per cent of the group, was due to the cardiac disease and might have contributed to the higher death rate. Susceptibility to infections was common in the children with congenital heart disease, but 23, including 1 cyanotic individual, survived attacks of pneumonia, 33 had had tonsillectomies, and several others had had operations of various kinds without any untoward effects.

**Patent Ductus Arteriosus—Prognosis**—Ligation of the patent ductus arteriosus in 11 patients has been reported by L. T. Bullock, J. C. Jones and F. S. Dolley.<sup>75</sup> In reviewing the general prognosis of untreated lesions of

this kind they found that 14 per cent of the patients had died before the age of 14 years, 50 per cent before the age of 30 years, and 71 per cent before the age of 40 years. Congestive failure, rupture of the ductus, and bacterial endocarditis were common causes of death.

Of their series of 11 patients operated upon, all but 1 recovered from the operation completely and showed improvement thereafter in respect to the increased amount of activity which they were able to endure without discomfort. They had less weakness, palpitation, fatigue, and dyspnea. The harsh to-and-fro murmurs were gone after operation, although some patients retained a soft systolic murmur; the thrill and the accentuated pulmonary second sound disappeared; and the diastolic blood-pressure increased to normal within 1 or 2 weeks after operation. The operation was more easily performed on the younger patients than in adults and it was believed that the benefits from the procedure would be greater in this age group.

The patent ductus arteriosus of a 7-year-old girl was obliterated by Gross, Emerson and Green.<sup>76</sup> Operation was performed without great difficulty and following it the murmurs and the precordial thrill disappeared, the diastolic blood-pressure became elevated, and there was a decrease in the size of the heart. The risk of the operation did not seem to be any greater than the complications, such as bacterial endocarditis, which might have occurred later if the patient had not been treated.

### Rheumatic Fever

**Etiology** — *Respiratory infections* bore a close relationship to first attacks of rheumatic fever and to recurrences of the disease in the children observed by Jones and Mote.<sup>77</sup> In 58 per cent of

a group of children, such infections immediately preceded the first attacks of rheumatic fever and in 66 per cent sore-throats preceded the attacks. In the remaining number of patients, however, no such infections were noted and the rheumatic fever seemed to occur spontaneously. Hemolytic streptococci could be recovered from some children who had no clinical evidence of symptoms involving the respiratory tract. Of the convalescent patients in inactive stages of the disease, who developed sore-throats, recurrences of rheumatic fever occurred in about one-half of the cases and in about one-third of those who had respiratory infections. Among all of the children who had recurrences of rheumatic fever, about two-thirds of the group had just recovered from respiratory infections.

**Diagnosis**—Various roentgenological methods for the determination of the size of the heart of rheumatic fever patients have been evaluated by Kuttner and Reyersbach.<sup>78</sup> For comparison they included the cardiac area, as determined from the teleoroentgenogram, the fluoroscopic examination of the patient in an oblique position to determine the angle of rotation necessary for the clearance of the left ventricle from the vertebral column, and, lastly, the deviation of the barium-filled esophagus caused by pressure of enlarged auricles or ventricles. A group of 101 normal children were compared in this manner with groups of children with potential heart disease or with mitral stenosis. The angle of clearance was increased in a large number of patients with mitral stenosis, in some with mitral insufficiency, and in a few with potential heart disease, but in the last group the determinations were unsatisfactory. In the patients with mitral stenosis the frontal cardiac areas were increased in a fairly large percentage of patients. Left auricular enlargement

could not be demonstrated in any of the children with systolic murmurs and was noted in only a few of the children who had mitral stenosis of several years' duration. Measurements of the frontal areas seemed to be the least accurate determinations of heart size and less valuable than the other methods. Most important of all was the necessity of following a case from time to time in order to detect changes in the size of the heart, rather than the attempt to make a diagnosis from a single observation alone.

The *Weltmann reaction* has been employed as a test of the activity of rheumatic infections in children by Klein, Levinson and Rosenblum.<sup>79</sup>

The reaction consists of adding various amounts of calcium chloride to blood serum which has been diluted 50 times and observing the point at which coagulation by heat occurs. Amounts of calcium chloride varying from 0.1 to .01 per cent of a 10 per cent solution were set up in a series of test tubes and equal amounts of diluted blood serum were added to each tube. The tube in which coagulation occurred indicated the amount of chloride solution necessary

In a group of patients with chorea the sedimentation rates were usually normal or slightly increased. The *Weltmann reaction* followed a similar course. In the patients with acute rheumatic arthritis and carditis, the sedimentation rates were rapid and the *Weltmann* values were low, but the latter tended to return to normal before the sedimentation rates. In patients with cardiac decompensation the sedimentation rate was nearer to normal levels, but the *Weltmann* values were elevated, depending upon the severity of the infection. The sedimentation rate seemed to be increased during both the exudative stages and the proliferative stages of rheumatic fever, while the *Weltmann* reaction was elevated only during the exudative stage

and returned to normal immediately afterwards. A combination of these 2 types of tests might give a more accurate picture of the stage of the rheumatic infection. It has served to differentiate other types of disease, such as subacute bacterial endocarditis from the rheumatic form.

**Prognosis**—The records of 685 children with rheumatic heart disease observed over a period of 15 years were reviewed by Stroud and Twaddle.<sup>80</sup> About 36 per cent of the group were attending school, 17 per cent were employed and about 6 per cent more were able to work but were not employed. Death had occurred in 21 per cent. Congestive heart-failure had accounted for the majority of deaths, while other children had died of acute rheumatic fever, bacterial endocarditis, embolism, and pneumonia. More than 80 per cent of the children had died before the age of 16 years, and at an average time of 3 to 5 years after the onset of their rheumatic disease. Among a group of 27 girls who became pregnant in later years, congestive failure at the time of delivery occurred in only 1 instance. Mild symptoms of circulatory failure occurred in 2 others during the pregnancy but they delivered their infants without any cardiac disturbance.

The course of pure *mitral stenosis* in 81 children and young adults has been followed by Walsh, Bland, and Jones.<sup>81</sup> Of this group 48 had been observed before the definite signs of the mitral stenosis developed. In the majority of instances, a period of 6 to 10 years elapsed from the onset of rheumatic fever to the development of the definite signs of mitral stenosis. In 14 patients the mitral stenosis was not present until 11 to 20 years after the initial attack of rheumatic disease. In the majority of instances the rheumatic fever attacks

had been mild in these patients and the authors concluded that mild forms of rheumatic fever led to the prolonged course of the disease and favored the development of pure mitral stenosis.

### Chorea

**Treatment**—Successful treatment of chorea and rheumatic infections by *fever induction* has been reported by Bauer.<sup>82</sup> A group of 70 children, 4 to 15 years of age, who had chorea were treated with the diathermy or with ty-

phoid vaccine to induce fever. There were 51 of these who had had cardiac lesions at some time during the period of observation. Only 18 patients required more than 1 course of treatment. In 2 instances, *collapse* occurred but the patients responded well to the administration of *adrenalin* and *ice compresses*. Improvement of chorea occurred rapidly in most instances and there seemed to be no deleterious effects upon other rheumatic manifestations or upon the heart disease.

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## INFANT FEEDING

By WALDO E. NELSON, M.D.

### Breast Feeding

A somewhat unorthodox plan for breast feeding has been recommended by Witkin,<sup>83</sup> who advises that young mothers express milk manually from each breast preliminary to feeding the infant in order to clear the lactiferous ducts, sinuses, and openings. He believes that this is more important and easier of execution than the more commonly practiced procedure of completely emptying the breasts after each feeding. It is stated that, once the outflow of milk becomes free and conditioned, the breasts take care of themselves and become adapted to the demands of the child.

Witkin also advises nursing from both breasts at each feeding. The mother is instructed to nurse the baby 8 to 10 minutes from one breast, and 5 to 7 minutes from the other. If the ducts and sinuses have been cleared by this preliminary expression, the author states there need be no fear of the breasts retrogressing as a result of not being "completely emptied."

**Breast vs. Artificial Feeding**—Observations on the relation of gastroen-

teric disturbances and rashes to various types of feeding have been made by Robinson<sup>84</sup> on a group of 240 infants for a period of 20 months. The incidence of diarrhea and of rashes was lowest in breast-fed infants. No advantage was observed in the use of lactic acid formulas in regard to such early feeding difficulties as colic, constipation, or regurgitation. Diarrhea occurred more frequently in infants fed whole milk than in those fed evaporated milk, and it was slightly more common in the infants receiving simple evaporated milk than in those receiving lactic acid-evaporated milk. This latter difference, however, was too small to be significant. Infants receiving irradiated milk had a somewhat higher incidence of rashes than those fed nonirradiated milk. All rashes cleared up without change of milk. The results are tabulated in Tables II and III.

### Soft Curd Milk

It is generally stated that cow's milk which has been treated in such a way that the curd size is smaller and softer and more nearly approaches that of

TABLE II  
INCIDENCE OF DIARRHEA IN INFANTS GROUPED ACCORDING TO TYPE OF FEEDING

Feeding	Sub- jects	Diarrheas		Severity			Quarter of Year			
		Num- ber	%	1	2	3	1	2	3	4
Breast	37	6	16.2	4	2	0	2	0	4	0
N. I. E.	30	16	53.3	11	4	1	1	6	6	3
N. I. E.—L. A.	24	10	41.7	7	3	0	2	2	4	2
E.—135	26	11	42.3	6	3	2	3	3	2	3
E.—135—L. A.	27	9	33.3	8	1	0	1	1	5	2
E.—200	30	11	36.7	9	2	0	1	1	9	0
E.—200—L. A.	21	10	47.5	5	5	0	2	1	5	2
W. M.—200—A.	25	13	52.0	11	2	0	3	1	5	4
Total	208	86	41.2	61	22	3	15	15	40	16
Average										

N. I. E. = nonirradiated evaporated milk.

N. I. E.—L. A. = Nonirradiated evaporated milk with 0.5 per cent lactic acid

E.—135 = irradiated evaporated milk, 135 U.S.P. units of vitamin D to the reconstructed quart.

E.—200 = 200 unit irradiated evaporated milk.

E.—200—L. A. = 200 unit irradiated evaporated milk with 0.5 per cent lactic acid.

W. M.—200—A. = 200 unit irradiated whole milk.

TABLE III  
RASHES IN INFANTS GROUPED ACCORDING TO TYPE OF FEEDING

Feeding	Sub- jects	Rash		Severity		Other Allergy	Family Allergy	Quarter of Year			
		Num- ber	%	Slight	Moder- ate			1	2	3	4
Breast	37	3	9.3	3	0	0	1	2	1	0	0
N. I. E.	42	5	11.9	4	1	1	2	3	0	0	2
E.—135	61	14	23.0	10	4	2	4	8	4	1	1
E.—200	51	7	12.9	7	0	1	2	3	2	1	1
W. M.—200	49	9	18.3	5	4	1	3	4	2	0	3
Total	240	38	15.8	29	9	5	12	20	9	2	7
Average											

breast milk is more readily digested. Curd size of milk may be reduced by such measures as preheating, preheating and homogenization as in evaporated milk, addition of acid, and by passing it through sodium-aluminum silicate, so-called "base-exchanged" milk (Lyman, Browne and Otting).

Reynolds, Macy and Sonders<sup>85</sup> have studied the degree of gastroenteric motility after ingestion of milks of different curd tension. Serial roentgenograms were taken after ingestion of pasteurized milk, evaporated milk di-

luted 1:1, and "base-exchanged" milk. Each was mixed with barium sulfate. The average gastric emptying times were 227, 214, and 193 minutes, respectively, for pasteurized, evaporated (diluted 1:1), and "base-exchanged" milks. The roentgenograms taken 10 minutes after ingestion indicated that the soft curd milks (evaporated and "base-exchanged") began emptying from the stomach in much less time than the pasteurized milk.

It is concluded that the more orderly progression of the soft curd milks

throughout the alimentary tract is in accord with the metabolic and clinical observations upon the nutritive advantages of the "soft curd milks."

Experience in the feeding of infants with milk treated with a *pancreatic proteolytic enzyme* just prior to pasteurization is reported by Blatt, Harris, Jacobs and Zeldes.<sup>86</sup> The addition of the enzyme so reduces the curd tension that boiling of the milk is unnecessary. The curds formed from this milk are soft, flocculent, finely divided, and tend not to agglomerate. The enzyme treatment does not alter the appearance, taste, or cream line of the milk. This milk has been fed to premature, newborn, and older infants in an institution during the past 3 years; it has been used either diluted or undiluted in accordance with

the usual methods of prescribing infant formulas. No evidence of milk intolerance was observed and curds were rarely seen in the infants' stools. It is suggested that the preparation of an infant's food with cold unboiled milk, cold water, and cold sugar solution eliminates the dangerous bacterial multiplication that occurs during the cooling phase of previously heated solutions. Elimination of boiling large quantities of milk also reduces the cost of preparation and refrigeration and materially increases the comfort of the workers in the milk laboratory. In the author's experience, infants fed this milk (enzylac) compare favorably with those in a control group fed formulas made from other milks and by other methods.

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## MEASLES

By ROBERT A. LYON, M.D.

**Etiology**—Measles virus has been cultivated on the chorio-allantois of the developing chick embryo by Rake and Shaffer.<sup>87</sup> Material was obtained from defibrinated venous blood and from throat washings of patients during the first day of the rash of the disease. The virus grown in this manner produced symptoms of measles in monkeys. The virus was found to be resistant to temperatures as low as 35° C. and to treatment with 10 per cent anesthetic ether at room temperature.

**Complications**—Encephalitis following measles has been observed in 13 children, 2 to 9 years of age, by Geiger and Sappington.<sup>88</sup> These patients con-

tracted measles during epidemics, involving more than 17,000 persons, in San Francisco during the years of 1935-36 and 1938-39. Prominent symptoms of the encephalitis which developed from 1 to 8 days after the onset of the rash were vomiting, headache, convulsions, irritability, rigidity of the neck, and accelerated pulse rate and cyanosis. The pressure of the cerebrospinal fluid was usually elevated, and the fluid contained larger than normal amounts of protein and numbers of mononuclear cells. Four patients recovered completely, 4 were improving at the time of discharge from the hospital, and 5 died, a fatality rate of 38.4 per cent.



## MUMPS

By ROBERT A. LYON, M.D.

**Complications** — *Meningoencephalitis* following mumps in 29 individuals has been reported by Tabor and Newman.<sup>89</sup> The incidence of this condition was found to be about 4 per cent of the hospitalized cases observed by the authors. In 2 of the 29 patients the symptoms of meningoencephalitis developed before the parotid swelling and in the others they developed at various times following the parotid involvement. The most common symptoms of the complication were nausea, vomiting, and severe headache. Rigidity of the neck occurred in various degrees in 26 of the patients and in 10 there was a positive Kernig reaction. Other reflexes were not abnormal except in occasional instances. In all but 2 of the patients there was an increase in the number of lymphocytes in the cerebrospinal fluid, the number of cells ranging from 100 to 1000 cells in most instances. Recovery usually occurred

within a week or 10 days. A follow-up study of 9 of these patients showed that 4 had persistent symptoms of irritability, nervousness, or a failure to do good work in school. One of the patients had experienced attacks of fainting and another had begun to have enuresis following the illness. The possibility of permanent involvement of the central nervous system with minor mental disturbances following such encephalitis was suggested by these studies.

**Treatment** — *Human convalescent serum* has been employed with success in the prevention of the spread of an epidemic of mumps by G. W. Kutscher, Jr.<sup>90</sup> In a summer camp a group of 51 susceptible boys who had been exposed to mumps received human convalescent serum in doses of 8 to 10 cc., depending upon their ages, on the fourth day after the original case was diagnosed. Only 1 of the exposed children contracted the disease.

## THE NEWBORN

By ROBERT A. LYON, M.D.

## Asphyxia

**Etiology** — Some of the etiologic factors contributing to neonatal asphyxia have been studied by Cole, Kimball, and Daniels.<sup>91</sup> The degree of asphyxia was determined by the condition of the baby at birth and the duration and amount of resuscitation which was necessary to establish independent breathing. Methods of resuscitation included aspiration of mucus with a tracheal catheter, the administration of carbon dioxide and oxygen mixtures, the injection of drugs such as coramine,

and the employment of artificial respiration. In a series of 5000 newly born infants the incidence of asphyxia was greatest in the premature infant. The incidence of asphyxia in the newborn was greater in first born infants; in infants of young mothers and of those over 40 years of age; in infants of mothers suffering from severe illness; in those suffering from trauma during delivery, and in those whose mothers had received large amounts of sedatives and general anesthesia during delivery. Some of these factors also caused a de-

crease in the gestation period and led to the delivery of premature infants.

The effects of *obstetrical analgesia* in the newborn infant have been observed by Kotz and Kaufman.<sup>92</sup> Their series consisted of 500 mothers who received paraldehyde alone or in combination with other drugs, 100 treated by barbiturates and scopolamine, 100 treated by other methods and, finally, 100 who received no analgesia at all. Infant mortality rates were 2.2 per cent of the group in which the mothers received paraldehyde analgesia and were 2 per cent and 1 per cent, respectively, in the other groups treated with drugs. These were gross mortality rates and it was impossible to say that the deaths were due to the analgesia itself. Respiration was delayed considerably in the newborn infants whose mothers had received paraldehyde. The first breath was taken on an average of 40 seconds after delivery in the paraldehyde group and in about 10 seconds in the other groups. There was no indication, however, that the delay in the initial respirations caused any subsequent damage to the infants who were followed in later years. Strange to say, the loss of weight, the incidence of fever, and dehydration were more frequent in the infants of the control group than in the group whose mothers received some type of drug.

### Congenital Defects

*Congenital cranial softening* has been studied by Reiss and Boder.<sup>93</sup> The condition has been given various names, such as *congenital craniotabes*, *cranio-malacia*, *vertex softening* and *osteoporosis*. In a series of 791 newborn infants, 32 per cent were found to have areas of cranial softening, occurring in the right parietal bone in 29 per cent, in the left parietal bone in 10 per cent.

and in both bones in 69 per cent. The condition was noted more frequently in infants born during the winter than in those born in the spring and summer when the hours of sunshine were greater. The percentage of frequency of the softening was twice as great in the negro race as in the white or Mexican race, and was greater in infants of young mothers, 15 to 19 years, who were primipara, and also in those of mothers who were older than the average. None of the 24 infants delivered in breech positions had the defect. Small infants had the defect more frequently than the larger and longer babies with the larger heads. Cranial softening occurred frequently in infants with facial asymmetry, soft cranial sutures, large anterior fontanelles and widely separated cranial sutures. Although the cranial softening was more frequent in the infants of mothers who had had diets low in calcium and phosphorus during pregnancy, there seemed to be a closer relationship between this condition and the lack of vitamin D intake of the mothers.

The incidence and course of *heart murmurs* in newborn infants have been investigated by Lyon, Rauh and Stirling.<sup>94</sup> Of a total number of 7673 newborn infants, heart murmurs were detected during the first week in life in 147, or 1.9 per cent. They occurred somewhat more frequently in the negroes than in the white infants, but there were no definite indications that sex, the month of birth or the birth weight had any influence on the incidence of the murmurs. Syphilis apparently played no part in the etiology of the condition. The majority of the murmurs were systolic in time and their quality was blowing or rough in an equal number of cases. The course of the condition could be followed in 92

infants of the entire group. Four of these had died and 2 were found at autopsy to have had congenital heart lesions. In the remaining 2 no autopsy was obtained and the cause of death was not definitely determined. Of the remaining 88 infants observed 6 months to a year after dismissal from the hospital, the murmurs had persisted in only 14 instances, or 16 per cent of the 88 infants who were followed. The presence of a defect of the interventricular septum was suspected in 3 but a definite diagnosis could not be made in the remaining number. When the incidence of congenital heart disease in older children was taken into consideration, the authors believed that the ordinary readjustments of circulation, occurring during the first few weeks of life, such as the persistence of patencies of the foramen ovale and of the ductus arteriosus, did not usually produce clinical cardiac murmurs. On the other hand, many of the infants who have true congenital defects of the heart probably do not have murmurs during the neonatal period but develop them in later months of life.

### Feeding

The *influence of complementary feeding* upon the weight of newborn infants and upon the subsequent success of breast feeding has been studied by Sanford.<sup>95</sup> A series of 4622 infants were observed over a 9-year period. During that time complementary feedings had consisted of protein milk, lactic acid milk, regular milk mixtures containing two-thirds parts of milk and one-third of water, or one-half milk and one-half water, with 5 per cent of added carbohydrates. Whether the infants received a complementary feeding or not, at least one-third of the group lost between 5 to 8 per cent of their weight at birth.

A complementary feeding given in addition to the regular nursing routine tended to diminish the average loss of weight, and a small number of the infants lost 10 per cent or more of their birthweight. The mixture consisting of two-thirds milk, one-third water and 5 per cent of added carbohydrate gave the best results as a complementary feeding in preventing the weight loss of infants. The infants who were breast-fed only, had a higher average of weight loss and the number who lost 10 per cent or more was greater than in the former group. The weight loss was reduced somewhat by giving 6 feedings instead of 5 feedings throughout a 24-hour period. The complementary feedings, however, tended to diminish the amount of breast milk secretion. Although a smaller per cent of the infants regained their birthweight by the tenth day of life when they were fed on the breast alone, this was the result of the greater drop in weight and was not due to the rate of gain thereafter. As soon as the milk secretion of the mother was established, the infants on the breast alone gained weight more rapidly than those who received a combination of breast milk and complementary feeding.

### Hemorrhage

The *incidence of intracranial hemorrhage* in the newborn was found to be about 0.7 per cent in more than 19,000 deliveries reviewed by Roberts.<sup>96</sup> This figure may have been too low because a large number of infants who died within the first 3 days of life had a diagnosis of asphyxia and other conditions and may have been due to intracranial hemorrhage. Some of the stillborn infants who were not subjected to autopsy investigation may also have died of this condition, especially

in the case of negro infants who were infected with syphilis more frequently than those of the white race. Intracranial hemorrhage occurred in 30 infants who were overweight, in 57 of average weight, and in 32 small infants. The condition was more frequent in infants of primiparas, in those born by abnormal deliveries requiring the use of forceps, and in those born with breech presentations. A series of 66 of these patients were followed in later life. All had had indications of intracranial lesions at birth but 60 per cent were entirely normal within 1 to 15 years after birth. Fourteen of the group had some definite motor or mental disturbances such as monoplegias, paraplegias, and spasticity. It was the conclusion of the author that 85 per cent of the babies with intracranial hemorrhage failed to survive the first 3 days of life, but that after this period such lesions rarely caused death. The diagnosis of Little's disease and cerebral spasticity could not always be traced to intracranial hemorrhage and it seemed probable that this condition was not due to birth injury but to a degeneration or malformation of the brain. It was interesting to note that such spasticities were rarely observed in the negro race.

### Icterus

The occurrence of *icterus neonatorum* could not be explained entirely upon the excessive destruction of red blood cells in the studies of Waugh, Merchant, and Maugham.<sup>97</sup> From the examination of the blood of a large number of newborn infants during the first 9 days of life, they noted an increase in bilirubin during the first 4 days followed by a fall towards normal levels thereafter. The appearance of clinical icterus of these infants was related somewhat to the blood content of bilirubin, since

the majority of infants with 5 mg. per cent of bilirubin or more tended to a yellowish discoloration of the skin and conjunctivae, but some infants with large amounts of bilirubin in the blood did not develop icterus while other infants with lower blood levels were definitely jaundiced. Hemoglobin values and the volume of packed cells tended to fall steadily throughout the 9-day period of observation, a trend which differed greatly from that followed by bilirubin levels. There was also no relationship between the amount of bilirubin in the blood and the original height of the hemoglobin, the fall in hemoglobin, and the volume of packed cells. Variations in the resistance of erythrocytes had no bearing upon the degree of bilirubinemia. These facts indicated a lack of correlation between the degree of icterus, the amount of bilirubin in the blood, and the development of bilirubinemia on one hand and the amount of blood destruction on the other. Although blood destruction does furnish an increased amount of pigment to be removed from circulation, the capacity of the liver to function properly must be reduced in order to explain the occurrence of icterus neonatorum.

A permanent injury which may have resulted from *icterus gravis neonatorum* has been described by Sobel and Zucker.<sup>98</sup> The patient, 3½ years of age, had suffered from a severe attack of icterus gravis neonatorum but was improving when symptoms of opisthotonos, choreiform movements, spasticity, and mental deficiency developed. At autopsy some of the nerve-cells had disappeared and others showed evidence of degeneration, rarefaction, and there was an increase in the amount of perivascular fat. These lesions were located most numerous in the cerebral cortex, and a decrease in the myelin

content and in the number of nerve-cells occurred in the globus pallidus and corpus subthalamicum. A lack of myelin was noted in the medulla at the lower end of the pyramidal decussation. Although these pathological findings are not characteristic of nuclear jaundice, the symptoms which the child displayed were typical of this disease and the author suspected that such cortical lesions and neurological deterioration might occur more frequently than hitherto noted in cases of severe icterus of the neonatal period.

### Infections

Infections of the *long bones* occurred shortly after birth in 3 infants observed by Cass.<sup>99</sup> In every instance, a *Staphylococcus aureus* was isolated from aspirated pus. The epiphyses involved were those of the sternoclavicular joints, the knees, wrists, and hands. The symptoms, which were rather mild in nature, included a swelling of the joints and a low grade fever. Roentgenograms usually demonstrated the destruction of the epiphysis; but following the treatment of repeated *aspiration* through the cortex, recovery was complete and surprisingly little deformity or disability remained. No other organs such as the lungs, skin, peritoneum, and meninges were invaded by the staphylococcus and the infants continued to gain weight throughout the illness.

The various types of *staphylococcal infections* of the newborn have been reviewed by Cass.<sup>100</sup> The most common sites of such infections were the eyelids and the umbilicus, and the characteristic exudate was a sticky secretion accompanied by crusts and local edema. Usually these infections were mild in their course, but occasionally they persisted for a considerable length of time and 1 child observed by the author died

as the result of persistent infection of this kind. Other staphylococcal infections produced paronychia and septic spots on the skin, such as pustules and abscesses. When the infection invaded the deeper layers of the skin to form a subcutaneous abscess, the danger to the infant was greater. Pemphigus neonatorum and Ritter's disease were thought to be caused by the staphylococcal infections and they seemed to spread like other contagious diseases. Osteomyelitis caused by the staphylococcus is rare in the neonatal period but has been reported. Staphylococcal pneumonia, followed by empyema, was observed by the author in 1 infant. Had the empyema not developed, the positive agent of the pneumonia might not have been determined and it seemed possible that the staphylococcus might cause pneumonia more frequently than is generally supposed. Meningitis caused by the staphylococcus is very rare in the newborn and recovery has been reported with the use of sulfanilamide. Septicemia is often overlooked in the newborn, according to the author, because the symptoms are not necessarily as severe as in the adult. A rapid loss of weight was a common symptom of this disease, when it was associated with other lesions in the body, such as abscesses or osteomyelitis. The staphylococcus is so widespread that it seems probable that many of the infections of the newborn are caused by this organism. In most instances the response of the infant has been good and the child makes a complete recovery, but in more severe types of the infection the septic lesions persist for a considerable number of days or weeks before the infant recovers. In overwhelming infections which occur in the infants who have little or no resistance, the symptoms consist of a toxic rash, high

TABLE IV  
DATA FOR FEMALES (CHART II)  
(J B McKittrick J Pediat)

	24-Hour Periods													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Maximum	160	109	99	99	111	120	105	114	110	100	118	105	114	100
Average	82	77	73	78	79	79	81	85	86	85	85	89	85	84
Minimum	55	59	54	52	54	43	54	67	62	65	58	63	62	70
Number of determinations	65	46	46	52	63	81	93	56	58	42	43	35	34	15
Number of infants	16	16	16	18	23	29	33	22	26	17	21	13	19	9

fever, poor appetite, and a rapid loss of weight, and the infant may not survive the infection.

The incidence of bacterial invasion of a group of 100 stillborn infants or those who died shortly after birth has been found to be 8 per cent in the study by Brim.<sup>101</sup> *Escherichia coli* was cultured from the liver or spleen in 5 instances and types of streptococci in 3 other cases.

### Physiological Variations

The instability of the blood sugar of newborn infants during the first 1 or 2 weeks of life has been demonstrated by McKittrick.<sup>102</sup> From the examination of blood samples of 73 normal newborns from day to day, he noted a general tendency for the blood sugar to drop during the first 2 days of life, with the lowest point usually reached by the third day. Values of 40 mg. per cent were frequently observed in the first weeks of life. During the second week of life there was a tendency for the levels to vary between 60 and 120 mg. per cent with an average between 80 and 90. By the end of the second week there was less variation. As a rule, the male infants had slightly lower blood sugar levels than female infants. In 1 infant born of a diabetic mother, the blood sugar dropped to a small percentage but the

subsequent determinations were not unlike those of the normal group. The author cautioned against the tendency of attributing death to hypoglycemia in such instances, since the normal trends are so variable and blood sugars may

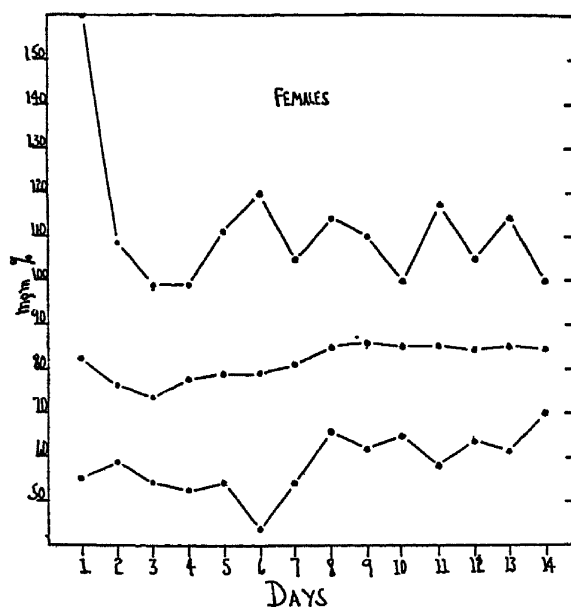


CHART II  
(McKittrick: J. Pediat.)

often reach low levels without any untoward symptoms.

*Dextrose tolerance* tests of the newborn have been reported by Ketteringham.<sup>103</sup> Fifteen normal infants were given oral administration of 1.75 Gm. of dextrose per kilogram of body weight and the blood sugar determinations were

TABLE V  
DATA FOR MALES (CHART III)  
(J. B. McKittrick, J. Pediat.)

	24-Hour Periods													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Maximum	113	102	93	109	109	111	110	109	113	109	105	109	103	99
Average	76	72	67	74	77	81	83	83	87	87	85	86	86	91
Minimum	45	45	45	43	53	56	54	55	66	67	59	69	68	83
Number of determinations	71	55	54	57	76	92	104	66	68	54	50	43	42	13
Number of infants	18	18	18	22	27	34	36	25	29	19	24	16	22	7

made 1, 2, 3 and 4 hours after the midpoint of administration of the dextrose. In every instance there was a rise in the blood sugar but none of the rises exceeded normal limits. In 11 of the group the amounts of sugar at the end of 3 hours were lower than the initial determinations, which illustrated the so-called hypoglycemic reaction of Foster. The fasting level was reached by the majority of the infants within 2 hours, and by the remainder within 3 hours. The group of infants who received milk formulas tended to reach maximum blood sugar levels within a half-hour after ingestion, while the breast-fed infants did not reach the peaks until 1 hour had passed. Dextrose tolerance curves of infants of diabetic mothers were difficult to obtain because these infants did not readily nurse or take their formulas. Their tolerance curves were more erratic and the results were not as reliable as in the normal group of infants. One such infant who had all the clinical signs of hypoglycemia was found to have repeatedly high levels of blood sugar and its dextrose tolerance was decreased.

*Variations in the red blood count of newborn infants depending upon the time of the ligation of the cord have been investigated by Frischkorn and Rucker.<sup>104</sup> In a series of about 400*

infants the umbilical cord was tied at varying intervals from 1 to 50 minutes after birth and blood counts were obtained. There was very little correlation between the red cell count of the infants and the number of minutes

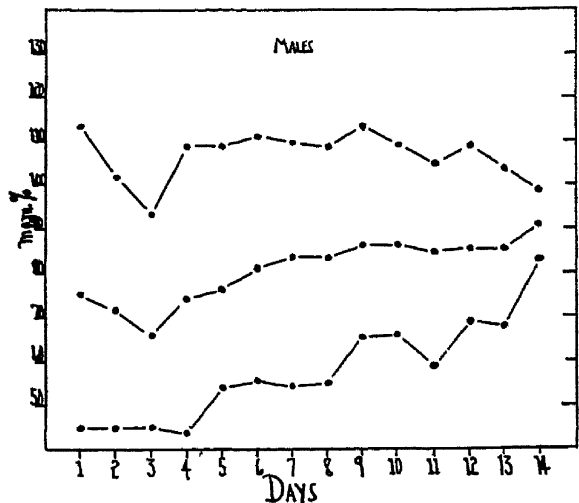


CHART III  
(McKittrick: J. Pediat.)

which elapsed before the cord was tied, but the infants whose cords were allowed to cease pulsating before they were tied had higher red counts than the infants whose cords were tied during the pulsating period. The average red cell count was about half a million greater when pulsation was allowed to cease before ligation. The pulsation seemed to drive the blood into the in-

fant and there was less blood left in the umbilical cord vessels.

*The intradermal saline test* might be used as an indication of the degree of *congenital edema*. In order to determine the absorption rates in the normal newborn, Shapiro<sup>105</sup> tested 60 infants during the first few days of life. The average time for the disappearance of the injected saline was 207 minutes, with ranges of 17 to 24 minutes in the majority of cases. There was no difference in the rate at which the material was absorbed in males or females and the values were not influenced by age, birthweight, or degree of weight loss during the first week of life.

### Prematurity

In a review of the subject of prematurity, Dunham<sup>106</sup> has stated that about 5 per cent of all live births recorded from various localities of this country have been premature infants weighing less than 2500 grams at birth. If a figure of 4 per cent was taken, it would mean that about 85,000 infants were born prematurely in 1936. The mortality rates of prematures are still very high. Of all of the causes of death in the first year of life, premature birth accounts for about 46 per cent and there has been very little decrease in this number over a period of many years. The mortality rates vary considerably, according to the weight of the child. About 6 to 14 per cent of the infants weighing 2000 to 2500 grams die, while those weighing from 1500 to 2000 grams have mortality rates of 22 to 45 per cent and those weighing 1000 to 1500 grams have rates of 57 to 84 per cent. Many attempts have been made in various parts of the country to improve the methods of treatment of premature infants by better facilities of hospital care and by providing

better methods of transporting premature infants to the hospital in portable heated boxes which prevent undue exposure and abnormal declines in temperature. Immediate care of the premature infants in both the hospital and in the home is an important factor, but it is also necessary to provide thorough supervision of the infant at home after he has been discharged from the hospital. The preparation of the home with adequate equipment and the education of the parents are duties of visiting nurses and physicians.

The factors leading to the death of 453 premature infants have been reviewed by Grier and Lussky.<sup>107</sup> Weight, parity, the type of labor, and obstetrical anesthesia were given especial attention. Mortality rates of the infants increased as the birthweight and their period of gestation decreased. Deaths were much more frequent in the male than in the female infants but other factors, such as parity, the length of labor, the type of delivery, and the use of sedatives and anesthesia had no definite effects on the mortality rates.

### Tetany

**Treatment**—The treatment of tetany of the newborn with *dihydrotachysterol* has been suggested by Bloxson.<sup>108</sup> This drug, which is a fraction of irradiated ergosterol, is supposed to increase the absorption of calcium from the intestinal tract and to assist in the excretion of phosphorus in the urine. The drug can be administered, as in the case reported by the author, in doses of 50 drops 3 times a day to infants who have small amounts of calcium in their blood serum. A method of determining the general status of the blood calcium is the measurement of the calcium in the urine. When the urine contains no calcium there is a



tendency for the blood serum levels to be low, *i. e.*, at a level producing tetany. When the calcium begins to appear in the urine, it is probably an indication of the rise in the blood calcium levels; when large amounts are present in the urine, there may be danger of hypercalcemia. The patient reported by the author was an infant 3 months of age who responded within 4 days after the drug had been administered. Roentgenologic examination of the long bones of this infant showed no abnormality.

### Placental Transmission of Drugs

The transmission of *sulfanilamide* from the mother to the fetus by way of the placenta and its effect on the fetus has been studied by Speert.<sup>109</sup> The drug, which was administered to rats in daily doses of 1 Gm. per kilogram of body weight throughout pregnancy, seemed to have markedly injurious effects on the offspring. Intrauterine and postnatal mortality were greater in the treated offspring; the litter size was smaller than normal; the average birthweights were less; and selective stunting was a common occurrence. The mothers ate and gained weight throughout pregnancy and did not seem to suffer any ill effects from the drug themselves, so that the injury to the offspring could not be explained on the basis of maternal malnutrition. The drug seemed to pass readily through the placenta of the rat. Although the conditions of the experiments were rigorous in that large doses of the *sulfanilamide* were given throughout the entire pregnancy, it seemed possible that some harm to the fetus of a human mother might result from the occasional use of the drug in the treatment of infections arising during pregnancy. The authors cautioned against the prolonged,

indiscriminate use of this form of therapy

### Avitaminosis

The variations in the *ascorbic acid* concentration in the blood of normal newborn infants during the neonatal period have been evaluated by Mindlin.<sup>110</sup> Concentrations of ascorbic acid were found to be considerably higher in the plasma of the infants than in the plasma of the mother in every instance. The average levels of the infants were 1.16 mg. per cent and of the mothers 0.42 mg. per cent. Shortly after birth the amounts of ascorbic acid in the plasma of the infant tended to diminish and usually reached their lowest levels on the third day of life. After that time the concentration of ascorbic acid in the newborn infants seemed to be dependent upon their diets. When an infant was breast-fed and received a milk rich in ascorbic acid, his blood levels tended to rise rapidly but rarely did they attain the heights of the initial concentration. When the ascorbic acid in the mother's milk was small in amount, the infant developed a correspondingly smaller percentage in his blood plasma. Ascorbic acid added to the mother's diet raised her blood plasma level and her infant obtained greater amounts from her milk. The drop in the concentration of ascorbic acid in the newborn infants did not necessarily mean that the tissues had been depleted of the vitamin, because the infant responded rapidly to ingestion of additional amounts of the ascorbic acid. It seemed probable that the various stages of this type of avitaminosis follow one another in the following order: The plasma level is first diminished and then there is a decrease in the ascorbic acid in the various tissues of the body; next there is a stage of asymptomatic scurvy in which there

may be demonstrated histologic changes in the tissues, and, finally, that period of clinical scurvy with gross pathological changes. The plasma levels alone, therefore, did not seem to indicate the degree of asymptomatic scurvy which might be present.

In their studies of *vitamin K*, Bray and Kelley<sup>111</sup> have noted that the *prothrombin time* in 23 newborn infants was near adult normal levels at birth but became prolonged in most cases during the second and third day and then gradually shortened to reach normal values by the fifth day of life. In 14 patients, the prothrombin time was never greater than 5 minutes and none of these infants showed any tendency towards bleeding. In 9 others the prothrombin times were longer than 5 minutes and 1 of these had a severe cerebral hemorrhage and died, while 3 others had evidence of bleeding in the skin or from cut surfaces. There was no relationship between the prothrombin times and the platelet counts of the infants.

A considerable decrease in the *prothrombin index* occurred within the first 48 hours of life in the series of newborn infants reported by Quick and Grossman.<sup>112</sup> The index of the prothrombin 6 hours after birth was relatively high and not very different from that of cord blood; at the end of 24 hours, however, there was a considerable decrease and then a gradual return to normal during the next 24 hours. In some instances the prothrombin levels did not return to normal until the fifth day of life. When the indices are low, vitamin K must be administered in order to prevent bleeding. The reason for the spontaneous rise in the prothrombin level is obscure. It would seem impossible that the small amounts of food taken by the infants in the first

1 or 2 days of life could be responsible for the increase in vitamin K which usually takes place.

In the study of the *prothrombin index* of mothers and newborn infants, MacPherson, McCallum and Haultain<sup>113</sup> found considerable variation in the levels during the first few days of life. In a group of 54 infants tested from day to day, decreases in the index began within 24 hours after birth which usually reached the minimum within 36 to 48 hours post partum. By the fifth day the levels tended to rise and gradually became stabilized at about 75 per cent. The prothrombin levels were not influenced by the type of labor or by the type of delivery. The average prothrombin index of maternal blood was above 75 per cent in the majority of the 15 mothers examined. Of 5 mothers with toxemia, 2 had normal prothrombin indices and 3 had deficient amounts. The cord levels of prothrombin were influenced by the maternal levels, but were usually 15 to 20 per cent less. The amounts in the cord blood seemed to be significantly lower when operative procedures were employed at delivery. The administration of vitamin K and related synthetic products tended to cause a rapid rise in the prothrombin index in the newborn. This change usually took place within 1½ to 2½ hours after intravenous administration. When given by mouth, the vitamin did not produce much of an increase until after 2 hours. Vitamin K given to mothers shortly before delivery raised the maternal and cord levels and also raised the levels within the infant's blood. The maximum benefits to the infant were achieved when the vitamin K was administered orally to the mother about 4 to 12 hours before delivery. In a series of 16 infants with symptoms of cerebral irritation and

low prothrombin indices, the administration of the vitamin raised the levels and led to an improvement of the symptoms in most cases. It was the conclusion of the authors that the vitamin should be given to the mother shortly before delivery or to the baby shortly after birth in all instances in which there was maternal toxemia, premature labor, difficult delivery, cerebral symptoms, hemorrhagic disease, severe icterus, anemia, in cases in which breast

The prothrombin levels of premature infants have been found by Hellman and Shettles<sup>115</sup> to be lower as an average than those of full term infants. The average levels expressed in dilution units were 102.5 for 18 mothers of full term infants and 126.9 for 9 mothers of premature infants. In spite of the higher maternal levels of the latter group, the premature infants had only 8.3 units as an average and the full term group 22.2 units.

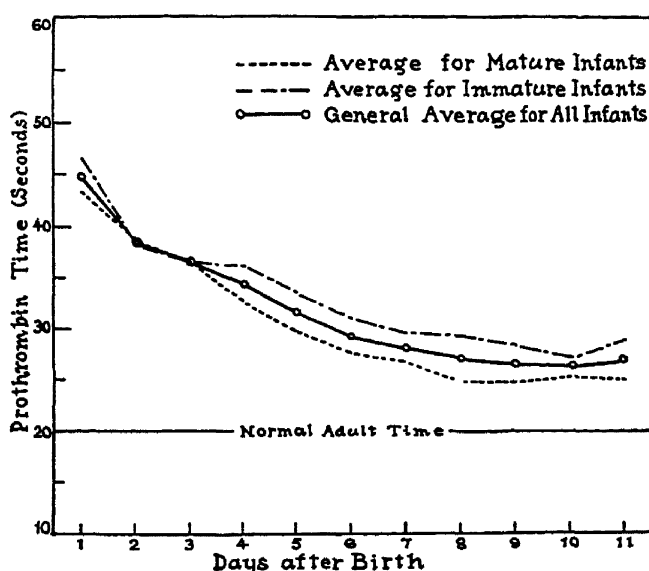


CHART IV—Average values for prothrombin clotting time in mature and immature infants during first 11 days of life. Cases with abnormally prolonged prothrombin time (over 2 minutes) have not been included in calculating these figures. (Kato and Poncher: J. A. M. A.)

feeding was impossible, and finally when operation of the newborn was necessary during the first few days of life.

Employing micromethods for the determination of the prothrombin levels, Kato and Poncher<sup>114</sup> found that the average clotting time of both mature and immature infants became shorter during the 10 days after birth. The clotting time of the blood of premature infants fluctuated much more widely during this period of time than did that of the mature infants, but approximately the same levels were reached by the tenth day by both groups.

The feeding of vitamin K to mothers before delivery and to their offspring was reflected by rises in prothrombin levels of the mothers and infants. Shettles, Delfs and Hellman<sup>116</sup> fed vitamin K to mothers for various lengths of time during the last month of pregnancy and noted that the levels of prothrombin in the infants were higher than those of a control group. These levels were maintained during the first week without the usual postnatal drop. Large doses given to a group of mothers within 24 hours before delivery caused elevations of prothrombin to 3 times that of

untreated patients. Administration of the vitamin to infants immediately after their birth caused elevations in their prothrombin levels but the rise was not equal to that produced by maternal ingestion.

*Seasonal variations in the vitamin K levels* in mothers have been noted by W. W. Waddell, Jr., and D. Guerry<sup>117</sup> A group of mothers tested in February and March had smaller amounts of the vitamin than a group studied in April,

The *relationship between prothrombin levels and hemorrhagic disease of the newborn* has been discussed by Quick and Grossman.<sup>118</sup> In their studies they found that the levels of prothrombin of the infants at birth were about 60 to 75 per cent of normal adult values. Soon after birth the levels tended to fall, reaching the lowest point during the first day of life. The results of others have shown that the low points are reached on the second or third day of

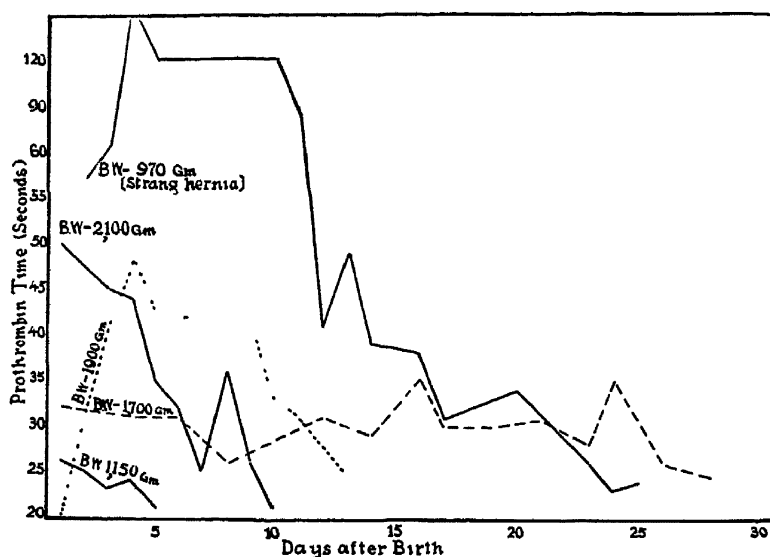


CHART V—Various types of prothrombin curves in individual babies  
(Kato and Poncher: J. A. M. A.)

May and June. The oral administration of *vitamin K* to a small series of mothers before delivery tended to increase the prothrombin index of their infants. The authors cited several case histories of infants with hemorrhagic tendencies who were definitely benefited by the administration of the vitamin. One infant, however, had a massive hemorrhage into the right pleural cavity and died.

This and other types of hemorrhage, especially those located in the brain, may be reduced in frequency if the treatment can be started early enough to serve as a protective measure.

life and tend to return to normal by the fifth day. Certain types of hemorrhagic disease of the newborn which are not due to specific diseases, such as hemophilia and the congenital absence of fibrinogen, are probably due to this sudden drop in the prothrombin levels of infants during the early days of life. The administration of the vitamin K to the infants usually raised the blood levels to adequate amounts for protection against hemorrhage. It is probable that intravenous transfusion accomplished somewhat the same result. No direct connection between jaundice of the newborn and their prothrombin levels has been observed,

in fact, some severely jaundiced infants have had normal levels of prothrombin.

The *relationship of feeding to the prothrombin content of the blood of newborn infants* has been studied by Salomonsen and Nygaard.<sup>119</sup> Twelve infants were given regular breast feeding 12 to 20 hours after birth and 13 infants were given extra feedings of a cow's milk mixture beginning 2 hours after birth. The latter group failed to develop the low levels characteristic of those who received breast milk alone. It was thought possible that the extra feedings might have hastened the bacterial metabolism which creates a supply of vitamin K.

From measurements of *plasma fibrinogen and prothrombin in maternal and cord blood*, Rush<sup>120</sup> found no relationship between these 2 substances. Both substances seemed to be present in normal amounts in the mother's blood at the time of delivery, but in the cord blood normal values of fibrinogen were sometimes accompanied by low levels of prothrombin.

Some difference of opinion has arisen concerning the *effect of storage on the prothrombin content of citrated blood*. This problem has arisen especially in regard to the storage of blood in blood banks and its subsequent value in the treatment of hemorrhage. Reinhold, Valentine and Ferguson<sup>121</sup> have found that prothrombin concentrations are reduced approximately one-fourth within

3 days after the blood has been taken. There is considerable variation, however, since some specimens showed no change at the end of this time while others showed a decrease of prothrombin to one-half of their original content. By 6 or 7 days, the prothrombin content decreased to approximately one-half of its original content and often remained in this state for long periods of time. Even after 3 to 5 weeks, 7 specimens had 48 to 53 per cent of their original content of prothrombin. Considering the fact that the blood is not usually kept for very long periods of time, and that large amounts are usually employed in intravenous transfusions, it seemed probable that adequate amounts of prothrombin would be obtained from the average transfusion.

The amount of *prothrombin in blood stored in blood banks* decreased to about 40 per cent of its original content over a period of 36 days, according to the observations of Ziegler, Osterberg and Hovig.<sup>122</sup> Considerable fluctuations in the prothrombin content of samples of such blood occurred from day to day but the general trend was downward over the period of time. Quick<sup>123</sup> also noted that decalcified blood which has stood for a period of time lost some of the prothrombin content and he concluded that fresh blood was more potent than preserved blood in controlling the bleeding associated with jaundice.

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## DISORDERS OF NUTRITION

By WALDO E. NELSON, M.D.

### Obesity

**Treatment**—The value of *benzedrine sulfate* in the management of obesity in children has been studied by Kunstadter.<sup>124</sup> Benzedrine sulfate was

administered to 30 obese children between the ages of 2½ and 16 years. These children were selected after they had failed to lose weight on a prescribed reducing diet. Many patients had re-

ceived thyroid extract in addition to the reducing diet. When benzedrine sulfate was prescribed, the average weekly weight-loss of 26 patients who had received continuous treatment for over 2 weeks was 0.831 pound per week. The greatest weight-loss occurred during the first 2 weeks of treatment. There was little or no variation in the basal metabolic rate during benzedrine treatment. The effect of benzedrine upon the pulse rate and the blood-pressure was variable. A slight fall in systolic blood-pressure occurred in 9 patients, a slight elevation in 4, and no significant change in 4 of the 25 patients on whom determinations were taken regularly. Two patients developed a marked bradycardia. Forty per cent of the children experienced unpleasant reactions at the onset of treatment. Withdrawal of the drug, however, was necessary in only 4 instances because of severe reactions.

The optimal effective dose of benzedrine sulfate for obese children was thought to be between  $\frac{1}{6}$  and  $\frac{1}{2}$  grain (10 and 30 mg.) per day. Weight-loss was primarily due to loss of appetite and subsequent decrease in food intake. Improvement in the state of mind with increase of will-power was thought to be a contributory factor. Withdrawal of the drug or decrease in the dose usually resulted in a return of appetite and an increase in weight. Tolerance for the drug developed frequently and required gradual increase in the dose. The authors point out that, although benzedrine sulfate is frequently an effective adjunct in the management of obesity in children, it is not a panacea. Social and psychologic adjustment, including improvement of the food habits, should be attempted during the course of treatment so that when the drug is discontinued, excessive food intake with regain of weight will not occur.

## Vitamin A

**Determination of Vitamin A in Blood**—A method for the determination of vitamin A and carotinoids in small amounts of blood has been described by C. D. May, K. D. Blackfan, J. F. McCreary, and F. H. Allen, Jr.<sup>125</sup> They state that the method apparently provides a direct clinical test for the early diagnosis of deficiency of vitamin A. In infants and children a deficiency of vitamin A may be detected by a low level of vitamin A in the blood before clinical signs appear. Even the earliest clinical sign of established deficiency of vitamin A, cornified epithelial cells, does not appear until the body stores are completely exhausted, when vitamin A is absent from the blood. Attention is called to the fact that when there is impairment of absorption of vitamin A, the amount of vitamin A and carotinoids in an ordinary diet is insufficient to prevent deficiency. In such instances administration of large amounts of vitamin A, *e. g.*, 50,000 U.S.P. units per day, preferably in divided doses, will result in the restoration of vitamin A storage. A large intake of vitamin A, however, must be continued as long as there is impairment of absorption if normal levels in the blood and normal storage in the tissues are to be maintained.

The relationship between *biophotometer tests* and the vitamin A content of the blood of children has been studied by Baum and McCoord.<sup>126</sup> No correlation was found between biophotometer readings and vitamin A content of the blood of 98 untrained subjects. The percentage of subnormal readings approximated that observed by Jeans when the authors' cases were regrouped by his standards. The decrease in number of subnormal readings found when trained subjects were tested indicates that the

TABLE VI

APPARENT ASCORBIC ACID CONTENT OF WHOLE BLOOD IN TERMS OF THE PLASMA, RED CELLS, AND WHITE CELLS—PLATELETS FROM SUBJECTS ON DIETS DEFICIENT IN VITAMIN C

Subject	Type of Deficiency	Volume per 100 cc Blood		Mg. Ascorbic Acid Equivalents per 100 cc. by Analysis				Calculated mg. Ascorbic Acid Equivalents per 100 cc. Whole Blood			
		Red Cells	White Layer	Plasma	Red Cells	White Layer	Whole Blood	In the Plasma	In the Red Cells	In the White Layer	Total by Addition
C	Acute scurvy . . .	35.0	1.0	0.0	0.0	3	0.0	0.00	0.00	0.03	0.03
	After vitamin C . . .	35.0	1.3	0.3	0.6	22	0.8	0.20	0.21	0.29	0.70
Y	Acute scurvy . . . .	33.7	1.1	0.0	0.0	0	0.0	0.00	0.00	0.00	0.00
	After vitamin C . . .	32.4	1.1	0.1	0.3	12	0.4	0.07	0.10	0.13	0.30
Ly	Acute scurvy . . . .	46.0	0.3	0.0	0.0	2	0.0	0.00	0.00	0.01	0.01
	After vitamin C . . .	51.0	0.4	0.0	0.0	12	0.0	0.00	0.00	0.05	0.05
	After vitamin C . . .	49.0	0.4	0.1	0.3	23	0.3	0.05	0.15	0.09	0.29
	After vitamin C . . .	50.0	0.3	1.0	1.1	38	1.3	0.50	0.55	0.11	1.16
Bl	3 weeks' experiment.	51.0	0.9	0.2	0.3	29	0.4	0.10	0.15	0.26	0.51
	4 weeks' experiment.	46.0	0.6	0.1	0.1	22	0.2	0.05	0.05	0.13	0.23
Cr.	3 weeks' experiment	49.0	0.6	0.2	0.2	28	0.3	0.10	0.10	0.16	0.36
	4 weeks' experiment.	49.0	0.5	0.1	0.1	26	0.1	0.05	0.05	0.13	0.23
	6 weeks' experiment.	47.0	0.4	0.0	0.0	10	0.1	0.00	0.00	0.04	0.04
	12 weeks' experiment	48.0	0.6	0.0		3	0.0				
G	Diet by history . . .		0.5	0.0		21	0.3	0.00		0.11	
Cer	Diet by history . .	37.0	1.1	0.0	0.2	12	0.2	0.00	0.07	0.13	0.20

training factor is important. They conclude that a single reading on the biophotometer is of no value in estimating vitamin A deficiency. However, the reading obtained by frequent testing with the biophotometer did not correlate with the blood vitamin A values in this series.

### Vitamin C

**Ascorbic Acid Distribution in Blood**—Observations on the distribution of ascorbic acid in whole blood and in various components of it, *i. e.*, plasma, red cells, white cells, and platelets, have been made by Butler and Cushman.<sup>127</sup> A summary of their results on subjects receiving diets deficient in vitamin C are shown in Table VI. On the basis of this study they conclude that the apparent ascorbic acid content of the whole blood, or of the white blood cells plus the platelets, of persons not suffering from infection or leukemia provides an

index of vitamin C deficiency that extends beyond the limits defined by plasma values. It is thought that the white cell-platelet concentration is less dependent upon fluctuation in plasma concentration than is the whole blood content. On the other hand, it is pointed out that white cell-platelet analyses will not provide maximal information concerning the saturation of subjects whose vitamin C nutrition is relatively good. It is stated that the apparent ascorbic acid content of red blood cells or of whole blood is a better index of saturation, as differentiated from unsaturation or deficiency.

**Vitamin C Nutrition**—A method for the determination of the state of vitamin C nutrition has been suggested by Kajdi, Light, and Kajdi.<sup>128</sup> It is pointed out that a single plasma vitamin C determination is not an adequate criterion of vitamin C nutrition. They advise em-

ployment of plasma ascorbic acid determinations before and again 4 hours after the intramuscular injection of 200 mg. of cevitamic acid which has been dissolved in 5 to 8 cc of physiologic saline solution. In their experience, plasma ascorbic acid values which are obtained 4 hours after the intramuscular injection of ascorbic acid and which are below 0.20 mg. per cent are indicative of scurvy, while those below 0.60 mg. per cent indicate serious depletion of the body depots.

In contrast to the relatively long periods of vitamin C depletion necessary for the plasma ascorbic acid concentration of adults to fall from the high value at saturation to low levels, Mindlin<sup>129</sup> has shown that the plasma ascorbic acid level of the newborn infant responds quite readily to changes in the ascorbic acid content of the diet. Thus, a short period of ascorbic acid starvation results in a prompt diminution in its plasma concentration. However, this does not necessarily signify depletion of the tissues to a similar extent. The prompt rise in plasma ascorbic acid concentration, which occurred in 1 of the infants in the author's series, with the resumption of only a moderate amount of dietary ascorbic acid indicates that no marked depletion of the tissues could have occurred in that interval. It is emphasized that the concentration of ascorbic acid in the plasma of the newborn infant is not a reliable index of the degree of asymptomatic scurvy which may be present.

**Supplemental Diets**—Further studies concerned with the effect of supplementing the diets of institutional children have been carried out by Roberts, Blair, Austin and Steininger,<sup>130</sup> and Roberts, Brooks, Blair, Austin and Noble.<sup>131</sup> In this study the diets of approximately 100 boys were supplemented with 2 to 3

bananas daily during the school year. The regular diet of the institution was considered adequate in that it fulfilled all minimum dietary standards which have been proposed. Nevertheless, it appeared to be susceptible to improvement, for the boys receiving the supplement showed consistently better growth and development by the various measures of physical status which were applied than did the control boys. These results indicate that the allowances for the various dietary essentials for boys of the ages studied should approach the higher rather than the minimum standards.

**Mineral Metabolism and Vitamin C**—A nutritional study which has implications beyond the scope of the particular problem involved has been carried out by Shepherd, Macy, Hunscher, and Hummel.<sup>132</sup> The purpose of this particular study was to observe the differences in mineral metabolism of normal children when they receive their vitamin C from different sources. These included synthetic ascorbic acid, an orange and lemon juice preparation with ascorbic acid added, and natural orange juice. Their results showed that the retention of nitrogen and minerals by the children was quite generally improved by substitution of fresh orange juice for the orange-lemon mixture. When  $\frac{1}{3}$  grain (20 mg.) of synthetic vitamin C (ascorbic acid) was added to the diets containing the orange-lemon mixture, only calcium retention was significantly improved and, although greater relative storage of cations to anions occurred, the total amount of positive and negative minerals stored was reduced. The most important observation made in this study is the recognition of the need for more extensive studies of the nutritional qualities of natural and comparable synthetic products in the diets of children. This would appear to be true not only



for vitamin C products but for other protective foodstuffs as well.

### Vitamin D

**Antirachitic Value**—A comparison of various prophylactic *antirachitic agents* has been made in the St. Louis area by Robinson.<sup>133</sup> This study is included since the results are somewhat at variance with reports that were included in this supplement on previous occasions in that rickets developed on dosages which have been reported by other observers as being antirachitic. The rachitic agents employed and the dosages administered are shown in Table VII. Two hundred and forty healthy infants were divided into 8 groups. The majority of these infants were studied for at least a year. Evidence of rickets was found in the roentgenograms of 33 per cent of the cases. Breast-fed infants receiving 5 drops of viosterol in oil daily (800 to 1000 U.S.P. units of vitamin D) were protected against rickets. In 1 of these, bone changes of active rickets developed 2 months after weaning. Viosterol in oil in a dose of 5 drops was not sufficient to give protection against rickets in infants fed nonirradiated milk. Irradiated milk containing 135 and 200 U.S.P. units of vitamin D to the quart did not protect against rickets. Two hundred units of whole milk was more protective than 200 units of evaporated milk. In most of the cases rickets healed spontaneously during the summer months without increase of vitamin D.

**Vitamin D Intake and Tooth Eruption**—The relation of quantitative variations in vitamin D intake to the age of the infant at the time of *eruption of the first deciduous incisor* has been studied by Speidel and Stearns.<sup>134</sup> The incisors of 22 infants given an intermediate vitamin D intake, from 300 to 400

TABLE VII  
GROUPING OF THE OBSERVED INFANTS  
ACCORDING TO TYPE OF FEEDING  
AND SOURCE OF VITAMIN D

Group	Feeding
1	Breast milk+viosterol in oil, 5 drops
2	Nonirradiated evaporated milk+viosterol in oil, 5 drops
3	Nonirradiated evaporated milk+viosterol in oil+lactic acid
4	135 unit evaporated milk
5	135 unit evaporated milk+lactic acid
6	200 unit evaporated milk
7	200 unit evaporated milk+lactic acid
8	200 unit fresh homogenized milk

units daily, showed the earliest mean age of eruption, 24.68 weeks. The eruption of the incisors of 17 infants with a low vitamin D intake, from 135 to 270 units daily, was delayed to a mean age of 28.29 weeks. The incisors of 6 infants with a high vitamin D intake, over 1800 units daily, also showed a delay in eruption, the incisors appearing at a mean age of 27.16 weeks. While these observations may point to a relationship, it must be borne in mind that only a small number of infants has been studied. Among 6 infants who had the 300 to 400 units intake, but who were subject to illnesses, the mean age of incisor eruption was 29.0 weeks. Although this group is small, these data indicate that illness delays tooth eruption and that the early eruption age is more nearly normal. It is noted that response of dental eruption to variations in vitamin D intake tends to parallel the responses of linear growth and mineral retention to the same influence during infancy.

**Effects of Vitamin D and Parathyroid Extract on Rickets Metabolism**—A study to determine the comparative effects of vitamin D, dihydrotachysterol (A.T. 10), and parathyroid extract on the disordered metabolism of rickets has been carried out by Albright, Sulkowitch, and Bloomberg.<sup>135</sup> The

metabolic effects of A.T. 10 and of the parathyroid hormone were studied on a patient with vitamin D-resistant rickets. A.T. 10 did not cause the marked rise in urinary phosphorus excretion which it causes in patients with deficient parathyroid glands. This difference is explained by the hypothesis that the other action of A.T. 10—to increase calcium absorption—leads to a decreased activity of the patient's own parathyroid glands which, in turn, leads to a decreased urinary phosphorus excretion. A.T. 10, however, did cause an increase in the urinary phosphorus excretion and did lead to an increased negative phosphorus balance. In these respects its action was different from that of vitamin D. These observations support the hypotheses which hold that both A.T. 10 and vitamin D have 2 actions, *i. e.*, to increase calcium absorption and to increase phosphorus excretion in the urine, but which also state that the ratio of the second of these actions to that of the first is greater with A.T. 10 than with vitamin D. The data also support the hypothesis that it is because of this difference alone that A.T. 10 is not anti-rachitic. The most striking effect of the parathyroid hormone was in increasing the urinary phosphorus excretion. On the basis of these data it is suggested that the action of vitamin D, A.T. 10, and parathyroid hormone on calcium and phosphorus metabolism can be depicted as follows:

	Calcium Absorption	Phosphorus Excretion in Urine
Vitamin D. . . . .	+++	+
A. T. 10. . . . .	+	+++
Parathyroid extract. .	0	++++

As one proceeds down the series—vitamin D, A.T. 10, parathyroid hormone—

the action on calcium and the phosphorus metabolism asserts itself more rapidly and lasts a shorter time.

#### Vitamin D Resistant Rickets—

There are now on record a few authentic cases of rickets occurring in children past the age of infancy in which the condition is resistant to vitamin D therapy but in which healing can be induced by

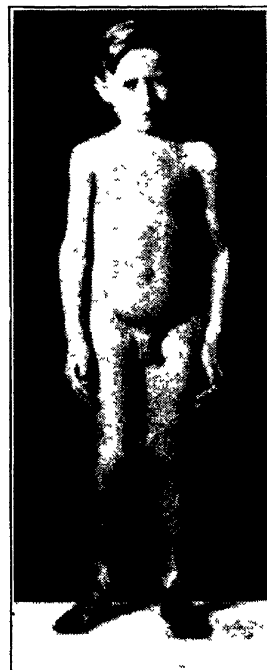


Fig. 4—W. D., in April, 1931, at the age of 8 years, 2 years after onset of illness. Note enlargements at wrists and ankles. (Bakwin, Bodansky and Schorr: *Am. J. Dis. Child.*)

*extremely large doses of vitamin D.* Another case of this type is reported by Bakwin, Bodansky and Schorr.<sup>136</sup>

A white boy, after an infancy and an early childhood which are described as normal except for repeated convulsions of undetermined origin, began at the age of 6 years to have difficulty in walking. At the age of 8 years, when the child was first observed, he had swelling of the wrists, ankles and costochondral junctions. Roentgenograms of the ends of the long bones showed changes characteristic of rickets. The shafts were well calcified. The value for serum calcium was about 11.0 mg., and for inorganic phosphorus about 2.0 mg. Renal function was normal and remained so during the entire period of observation.

Despite treatment with vitamin D in fairly large amounts (up to 40,000 U per day), ultraviolet radiation, calcium diphosphate, calcium gluconate administered by mouth and intravenously, alkalies and dihydrotachysterol, the boy became progressively worse until he was finally unable to stand without support.

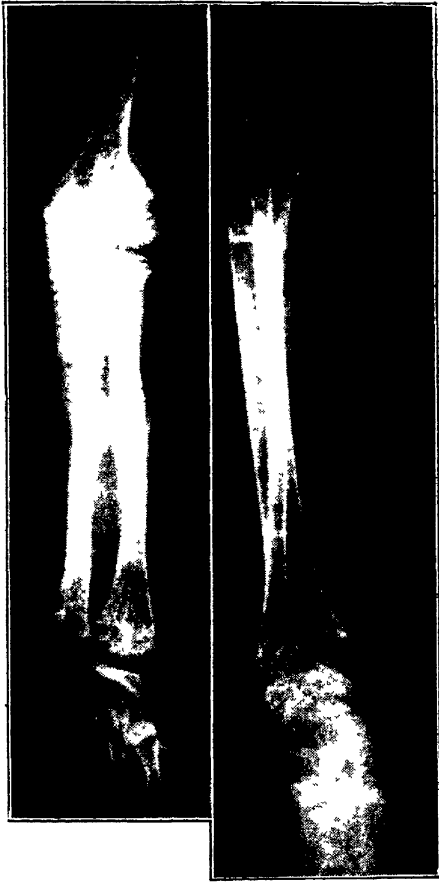


Fig 5—Roentgenograms of forearms, wrist and leg of W. D. made in December, 1937, 8 years after the onset of rickets. Epiphyses are irregular and show some deposition of calcium in rachitic zone. The bones, particularly of leg, show marked osteoporosis. (Bakwin, Bodansky and Schorr: *Am J. Dis. Child*)

At that time roentgenograms showed progressive decalcification of all of the bones. The parathyroid regions were explored, but no parathyroid tissue was found. Examination of the blood for vitamin D revealed that large amounts were being absorbed.

During the 7 years that the boy was under observation the serum calcium fell from an initial value of 11.0 mg. to about 10.1 mg, and the serum phosphorus from 2.0 mg. to 1.5 mg. The value for serum phosphatase, about 45 units in 1933, rose to over 70 units

in 1937. When the boy was receiving no extra vitamin D, the calcium and phosphorus balance showed poor retention, most of the ingested calcium being lost in the stool; after large dosages of vitamin D (40,000 and 110,000 units daily) there was good retention of calcium and phosphorus. After the administration of massive doses of vitamin D (1,000,000 units daily), the rachitic changes disappeared and the serum calcium, phosphorus, and phosphatase returned to normal levels. The boy remained normal except for his rachitic deformity, but it was necessary for him to continue large amounts of vitamin D to prevent relapse.

### Amino-Acids

Studies to determine whether the nitrogen metabolism of the body can be satisfied by the *oral* or *parenteral* administration of the amino-acids of hydrolyzed casein are being carried out by Shohl,



Fig. 6—W. D. in 1938, at age of 16 years, after rachitic healing. Height was 132 cm. (Bakwin, Bodansky and Schorr: *Am. J. Dis. Child.*)

Butler, Blackfan, and MacLachlan.<sup>137</sup> This is apparently the first attempt to feed human beings with amino-acids as the sole source of nitrogen. It has been shown previously by other workers that

casein at a level of 8 to 18 per cent of the dry diet provides adequate protein intake for rats. In this study the authors proposed to ascertain whether the amino-acids derived from casein were adequate for nutrition so far as could be determined by nitrogen balance measurements over short periods of time. The product em-



Fig. 7—Roentgenogram of W. D. made in July, 1938, showing complete healing after massive doses of vitamin D. (Bakwin, Bodansky and Schorr: *Am. J. Dis. Child.*)

ployed was an enzymatic hydrolyzate of casein which contained 11.9 per cent of nitrogen, of which over 60 per cent was present as amino-acids. No protein was demonstrated by chemical tests. The absence of native casein was also shown by negative sensitization tests on guinea-pigs.

The amino-acids when supplemented with the non-nitrogenous dietary essentials gave positive nitrogen balances in all instances. It was also found that positive and sufficient nitrogen balances

were obtained by the intravenous administration of hydrolyzed casein together with glucose and sodium chloride. In most instances, however, there were untoward reactions, most prominently an elevation of body temperature. The authors emphasize that further study is necessary to identify and remove the cause of these febrile reactions, which in their experience have limited the clinical utility of this form of intravenous nutrition.

Subsequent studies by Shohl and Blackfan<sup>138</sup> demonstrate that positive nitrogen balances of the same degree are obtained by *intravenous* administration of similar amounts of a crystalline amino-acid mixture and of casein hydrolyzate. It is of interest that the nitrogen balances were comparable with these 2 products since nearly one-fourth of the amino-acids of the crystalline product were in the inactive form. The rise in temperature which sometimes accompanies the intravenous administration of amino-acids occurred as frequently with casein hydrolyzate as with crystalline amino-acid mixture.

### Carbohydrate Requirements

Studies have been carried out by Heymann<sup>139</sup> in an effort to explain the relatively greater carbohydrate requirement of infants and children. It is pointed out that the normal diet of the breast-fed infant at 3 months of age contains, in percentage of total calories per kilogram of body weight per day, about 4 times more carbohydrate than the normal diet of a 6-year-old child and 10 times more than the diet of an adult. To throw some light on the reasons for these differences, the glycogen content of liver and muscle tissue was determined for normal and for fasting animals 8 to 11 days old, 10 to 12 weeks old, and 2 to

3 years old. It was observed that the livers of 6- to 8-day-old rats, rabbits, and dogs contained one-half to one-quarter of the amount of glycogen per 100 grams of fresh tissue as did the livers of older animals. The author thinks it unlikely that the high rate of glycolysis in liver tissue of baby rats and human infants causes the low storage of glycogen in the liver because neither the cortex nor the medulla of the kidney showed a similar diminution in glycogen content in spite of a similarly high rate of glycolysis in the kidney tissue.

While the underlying metabolic differences between infants and adults are not apparent from these studies, some of the reasons for the higher carbohydrate requirement of infants and children appeared to be: (1) For *infants*, (a) hypoglycemia is easily produced by carbohydrate starvation, (b) the presence of low glycogen reserves in the liver, and (c) the importance of carbohydrate for water retention. (2) For *children*, (a) hypoglycemia is easily produced by carbohydrate starvation, and (b) the pronounced tendency to ketosis.

## PARASITIC DISEASES

By WALDO E. NELSON, M.D.

**Incidence**—A recent survey to determine the incidence of intestinal parasites in children of Toronto by Kuitunen-Ekbaum<sup>140</sup> is of interest because of the high rate of infection. Of 438 children, 147, or 33 per cent, were found to harbor 1 or more species of protozoa or helminths as shown in Table VIII. A pinworm survey of 843 children was made in 3 separate medical institutions. The average percentage of infection for all age groups was found to be 48.63. In view of these data, the question might well be raised whether the incidence of intestinal parasites in children is much more frequent than generally believed.

### Giardiasis

Further observations by Véghelyi<sup>141</sup> convince him that *Giardia lamblia* are in some instances pathogenic for man. The 3 characteristic manifestations are said to be abdominal complaint, anemia, and retarded development. It is his opinion that the symptoms of children infected with *Giardia lamblia* are due to disorders of absorption. He believes that the para-

TABLE VIII  
SPECIES OF PARASITES FOUND IN CHILDREN  
IN TORONTO

<i>Species of Parasite</i>	<i>Number of Instances</i>
<i>Blastocystis hominis</i> . . . . .	47
<i>Chilomastix mesnili</i> . . . . .	9
<i>Giardia lamblia</i> . . . . .	41
<i>Trichomonas hominis</i> . . . . .	3
<i>Endamoeba histolytica</i> . . . . .	4
<i>Endamoeba coli</i> . . . . .	55
<i>Diendamoeba fragilis</i> . . . . .	2
<i>Endolimax nana</i> . . . . .	15
<i>Iodamoeba buetschlii</i> . . . . .	3
<i>Diphyllobothrium latum</i> . . . . .	1
Species of <i>Taenia</i> . . . . .	1
<i>Ascaris lumbricoides</i> . . . . .	5
<i>Trichocephalus trichiurus</i> . . . . .	1
<i>Enterobius vermicularis</i> . . . . .	16

sites practically cover the active surface of the intestine and interfere with absorption by forming an impermeable layer. The degree of impairment is thought to be proportional to the area of intestinal surface rendered inactive. If this surface is small, the capacity for absorption may remain adequate, and no symptoms arise. This is thought to be

TABLE IX  
RESULTS OF BLOOD COUNTS IN 3 CASES OF TRICHINOSIS

	May 8, 1938						May 20, 1938			
	Hemo- globin %	No of Red Blood Cells	No of White Blood Cells	Poly- mor- phonu- clears %	Lym- pho- cytes %	Eosino- phils %	No. of White Blood Cells	Poly- mor- phonu- clears %	Lym- pho- cytes %	Eosino- phils %
J. M.	80	5,370,000	16,500	57	7	36	12,600	27	22	51
R. M.	80	4,210,000	15,100	63	24	13	12,900	30	29	41
F. M.	75	4,610,000	17,100	77	12	11	9,900	34	36	30

the explanation of the fact that in many instances infected persons show no symptoms. On the other hand, infections may be severe enough to cover extensive intestinal surfaces, thus leading to a condition similar to atrophy from inanition. The state is further aggravated by the fact that besides foodstuffs, other important substances, such as bile and vitamins, are not absorbed, and also that a great part of the available supply of calcium and magnesium is expended in binding the excess of free fatty acids. Absorption of fat and excretion of bile pigment in the urine were examined in 17 children infected with *Giardia lamblia*. None of them showed evidence of disease other than the parasitic infection. Fat absorption was found to be greatly defective, and only a small part of the normal amount of urinary pigment was excreted. The resulting difficulty in absorption gave rise to symptoms of anemia and retardation of development. All the symptoms disappeared after the expulsion of the parasites. The fat absorption in the intestine and the pigment content of the urine became normal, anemia improved, and rapid growth

ensued. *Acetarson* and *acridine compounds* were used in treatment.

### Trichinosis

**Diagnosis**—The importance of looking for larvae in the blood of patients suspected of having trichinosis is emphasized by the report of Failmezger and Spalding.<sup>142</sup> Three children of a family of 6 were admitted to the hospital on the same day. All 3 patients were acutely ill and had pain and soreness in the back and in the extremities, associated with fever and with edema of the face and the eyelids. The blood counts are shown in Table IX. The intradermal test was performed with trichinae antigen. Negative results were obtained in all 3 children, 9 and 18 days, respectively, after their hospital admission. The diagnosis of trichinosis was proven by finding the larvae in the blood of all 3 patients by the method described by Kolmer, Boerner and Garber, in which 10 cc. of venous blood is mixed with 25 cc. of a 2 per cent solution of acetic acid and centrifuged thoroughly and the sediment is examined directly or by smears stained with Wright's stain.

## POISONING IN CHILDREN

By WALDO E. NELSON, M.D.

**Alcohol — Treatment** — Successful treatment with *insulin* and *glucose* of acute alcoholism in a small child is reported by Taylor and Cross.<sup>143</sup> The treatment is based upon experimental observations that the toxicity of alcohol is inversely proportional to the level of the blood sugar. Thus, in rats the lethal concentration of alcohol is 20 per cent higher when the blood sugar level is 100 mg. per cent than when it is 70 mg. per cent. It has also been shown that in rabbits the utilization of alcohol by the organism is a function of the concentration of blood sugar and is affected by insulin.

The child, a colored male 3¾ years of age, had drunk ½ pint (250 cc.) of rubbing alcohol and was comatose when admitted to the hospital. Two intravenous injections, each consisting of 5 ounces (150 cc.) of 10 per cent glucose, were administered and 10 units of insulin were given intramuscularly with the latter administration of glucose.

**Bromide**—Two instances of bromide intoxication in 3- and 4-year-old children, respectively, are reported by Harris.<sup>144</sup> In both instances the evidences of bromide intoxication were observed after fairly long periods of medication with sodium bromide; 1 child had received 15 grains (1 Gm.) 4 times per day and the other, 15 grains (1 Gm.) 3 times daily. Bromide intoxication in infants and children has been practically unknown although it is not uncommon in adults. It is quite possible, however, that it occurs more frequently in children than is generally supposed and that there is a failure to recognize the relationship between the clinical course and its cause.

The *symptoms* of bromide intoxication, while varied, are described as pre-

senting a fairly definite clinical syndrome. The onset is apt to be insidious. The first symptom is an unusual hyperexcitability; the bromide medication may be increased to counteract this complaint. In addition there are a slurring of speech, uncontrollable generalized tremor, and difficulty in walking due to a marked ataxia. There may be hallucinations, both auditory and visual. If intoxication is severe, there may be stupor, or even coma and death. Swallowing may be difficult and the mucous membranes dry. The pupils may be unequal and react sluggishly to light. Superficial reflexes may be absent and deep reflexes diminished. There may or may not be an elevation of temperature. There is usually no rash. This is an important point as, in the absence of the characteristic cutaneous lesions, the possibility that bromides are the cause of the psychic and neurologic changes is even more apt to be overlooked.

The *diagnosis* is established by determination of the bromide concentration in the blood. The level of the blood bromide concentration at which toxic manifestations occur has been arbitrarily set at 150 mg. per 100 cc. of blood.

**Ephedrine**—An instance of ephedrine poisoning in an infant 5 months of age, in which the clinical picture showed a combination of features common to both atropine and to strychnine poisoning, is reported by Lapin and Weichsel.<sup>145</sup> Instructions had been given by a physician to instill 2 drops of a 3 per cent aqueous solution of ephedrine sulfate into each nostril of the baby at intervals of 4 hours. The mother, however, had instilled the drug practically at hourly intervals so that at least 20 doses

had been given within a period of 36 hours. At this time the mother noticed extreme nervousness and irritability of the infant. The examination shortly afterwards revealed an acutely ill child, lying in the position of opisthotonos. There were paroxysmal contractions of the musculature, lasting for several seconds and appearing at intervals of about 10 minutes. There was marked tonic spasm between these paroxysms. The temperature was 101° F (38.3° C); the face was pale, the skin was cold and clammy. The deep reflexes were increased, the pupils were widely dilated; the palatal reflexes were absent, and the child could not, or would not, swallow.

The *treatment* consisted of *morphine sulfate*  $\frac{1}{64}$  grain (1 mg.) hypodermically and a *gastric lavage*. The symptoms disappeared after a period of 8 hours.

**Lead—Glycosuria** is not an infrequent occurrence in children with lead poisoning. Studies to determine the cause of the glycosuria in this condition have been made by Goettsch and Mason<sup>146</sup>. In the case studied by them the glycosuria persisted for 5 weeks, the concentration of urinary sugar decreasing as convalescence progressed. The level of

the blood sugar was consistently normal or lower than normal, and the urinary concentration of sugar remained relatively constant irrespective of the diet. In view of these findings, they suggest that the glycosuria in lead poisoning is renal in origin and may be classified as *renal glycosuria*. In a survey of 8 cases of lead poisoning with glycosuria, the blood sugar values were normal in 5; in 3 cases in which dextrose tolerance curves were obtained, the curves were not of the diabetic type. Glycosuria did not appear to alter the prognosis in these cases of lead poisoning.

On the basis of their experience, Haverfield, Bucy, and Elonen<sup>147</sup> state that the acute manifestations of *lead encephalopathy* can be relieved by *surgical decompression*. They believe that surgical decompression of the brain may not only be a life-saving measure but may be instrumental in preventing such sequelae as mental retardation, paralysis, tremors, and disturbances of vision. General and not local anesthesia should be employed during operation in these cases. Apparently either a suboccipital or a subtemporal decompression may be effective. Which will be employed must depend upon the exigencies of the case.

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## POLIOMYELITIS

By ROBERT A. LYON, M.D.

**Incidence**—The incidence of poliomyelitis, reported by Dauer<sup>148</sup> during the year 1938, was 1.3 per 100,000 population. In 1939 the number of cases was 7331, or a rate of 5.6 per 100,000 population. During this latter year, the highest rates occurred in Arizona, New Mexico, South Carolina, and Minnesota, and slightly lower rates in Michigan, Utah, and California. In isolated com-

munities, rates of 30 or more per 100,000 population occurred.

**Bulbar Paralysis**—An epidemic of poliomyelitis which included an unusually large number of bulbar cases has been reported by Stebbins, Gillick and Ingraham.<sup>149</sup> Of a total of 20 cases of poliomyelitis, 13 were afflicted with bulbar paralysis and 12 of these died, a fatality rate of 60 per cent for the entire



epidemic. The ages of these patients varied from 4 months to 21 years. In only 2 of the bulbar cases had tonsillectomy been performed; in 1 case, 2 weeks preceding the onset of the disease, and in the other 4 years previously. A search for contributing factors yielded no definite evidence of a vector or the contamination of any substance with which the group had contact.

**Effects on Mentality**—No abnormal effects of poliomyelitis upon the subsequent mentality of a group of patients could be detected by Gordon, Roberts and Griffiths.<sup>150</sup> Stanford-Binet tests were administered to 98 children who had recovered from poliomyelitis 11 months to 15 years previously. The curve of distribution of the results followed very closely the normal curve of distribution for that type of population. The sex and the age of the patients at the onset of the disease did not influence the intelligence levels. The interval between the time of the infection and the time of the testing was inconsequential, and the occurrence of cerebral symptoms during the attacks likewise had no effect upon intelligence. The authors called attention to the fact that the deprivation of the child from school because of the prolonged convalescence from poliomyelitis and the crippling effects of the disease might produce personality changes and emotional disturbances simulating mental retardation.

**Second Attacks**—In poliomyelitis these may be due to infection with different or more virulent strains of the virus. Employing a virulent virus isolated by Flexner from a patient of the Philadelphia epidemic of 1932, Toomey<sup>151</sup> was able to produce poliomyelitis in monkeys which had had previous attacks of the disease or had resisted the infection of heterologous types of poliomyelitis virus. Even animals which

had recovered from severe infections of poliomyelitis virus were observed to contract second attacks of the disease when inoculated with large doses of the Philadelphia virus.

**Methods of Infection**—The *intracutaneous* route of poliomyelitis infection is probably very uncommon, according to the observations of Stimpert and Kessel.<sup>152</sup> They were able to infect some monkeys by the intracutaneous injection of certain virulent strains of the virus but the results were not constant. The degree of immunity which the monkeys developed by this type of injection varied considerably, and was not related to the virulence of the strains injected.

The virus obtained from *human stools* has infected chimpanzees when it was administered by several portals of entry. Howe and Bodian<sup>153</sup> inoculated 3 animals by introducing the material into the stomach with a stomach tube on 5 successive days. Two other animals had their olfactory tracts cut and then were given the stool material intranasally and by mouth. All except 1 of the entire group of 5 chimpanzees contracted poliomyelitis, so that the nose, mouth and stomach seem to be portals of entry of the virus in this particular species of animal.

Toomey<sup>154</sup> has been able to isolate the virus of poliomyelitis from the *stools* of patients with that disease but he was unable to obtain the virus in this manner from 2 experimental animals who had been injected intracerebrally with the virus.

The virus of poliomyelitis has been recovered from the *stools of healthy contacts* by Kramer, Gilliam, and Molner.<sup>155</sup> In an institution in which several patients developed poliomyelitis, the stools of 3 of a group of 12 healthy children who were exposed were found to contain the virus. Three other chil-

dren who had some fever but no other clinical signs of the disease, and 1 healthy adult who had been caring for the children also had the virus in their stools. In 2 patients the virus was recovered twice at intervals of 19 days.

Further work verifying the presence of poliomyelitis virus in human stools has been reported by Paul, Trask and Vignec.<sup>156</sup> Of an entire group of 53 patients, in the first 4 weeks of their illness, 8 had stools in which the virus could be detected. The virus could be obtained in any of the first 4 weeks of the disease but was not obtained in later periods. The virus occurred more often in the stools of children 2 to 5 years of age than in older patients and was recovered most frequently from patients with nonparalytic types of disease. The stools of patients suffering from other infections did not contain the virus nor did those of 8 healthy individuals who had been in close contact with the infection.

The presence of the virus in the *sewage* of 3 large cities during 7 epidemics of poliomyelitis has been detected by Paul, Trask and Gard.<sup>157</sup> The virus could be recovered most readily in sewage samples taken close to isolation hospitals. It seemed probable that the virus was viable for a distance of at least 300 feet in the flowing sewage and that large quantities of virus might be present at certain times.

**Treatment**—The *mechanical respirator* has been a valuable instrument for the treatment of *respiratory paralysis* following poliomyelitis. The results of its use have been reviewed by Wilson.<sup>158</sup> The several types of paralysis which may be caused by poliomyelitis include that of the intercostal muscles and of the diaphragm, a disturbance of the nerve centers of respiration in the medulla, and finally the

collection of mucus in the pharynx accompanying paralysis of the local muscles. Good effects from the respirator can hardly be expected in types of bulbar or medullary paralysis and many of the unfavorable results and deaths which have resulted in spite of the use of the respirator do not indicate that the method is valueless. In cases in which the intercostal muscles or diaphragm are involved, the patients may profit well by the use of the instrument. The purpose of the respirator is to give rest to the affected muscles and the author stressed the importance of the early detection of signs of weakness of muscles of respiration and the immediate use of the respirator in such cases. He described 2 or 3 other types of mechanical respirators which have been suggested. One was the development of a large respirator which could accommodate several persons at a time and would allow for more movement of the patients. Another type was a smaller contrivance in the form of a jacket which would fit tightly around the chest and provide immediate relief for a patient besides allowing considerable more freedom of movement. Also of importance is a co-ordinated program which would provide facilities for mechanical respiration for a larger portion of the population. If the expense of the equipment could be shared and duplication avoided, many more communities could derive benefit from the respirators.

The advantages of the *underwater exercises* for children with poliomyelitis have been reviewed by Hansson.<sup>159</sup> A total number of 54 patients with various types of paralysis were treated by the underwater method, while another group received the usual therapy of heat, massage, electrical stimulation and muscle re-education. No differ-

ences in the percentage of muscle recovery were noted in the 2 groups but the pool gave the patients a sense of security and a great deal of pleasure while they were carrying out the exercises, and were receiving massage and muscle re-education. The author emphasized the fact that during the *acute phase* of the disease the immobilization of the muscles with *plaster casts* was necessary, but in the later stages the underwater treatment provided a moist application and seemed to promote the relaxation of the muscles, caused less over-stretching of the weakened muscles, and allowed the exercises to be performed with greater ease than on a table. At the proper time, walking was more easily attempted first in the pool with the aid of the buoyancy of the water, than outside with crutches and braces.

Indications that *vitamin C* may inhibit the action of poliomyelitis virus have been noted by Jungeblut.<sup>160</sup> *In vitro*, the addition of synthetic *ascorbic acid* to virulent poliomyelitis virus so changed the virus that it did not cause infection in monkeys. When the vitamin was instilled intranasally into monkeys along with the virus, constant results were obtained. Infection caused by the flooding of the nasal passages with the virus was not affected by instillations of vitamin, but slower administration of the virus and vitamin

together into the nose gave various results but suggested that the ascorbic acid might have attenuated the attacks of poliomyelitis.

*Neoprontosil* has been employed in the treatment of children with poliomyelitis during an epidemic occurring in Charleston, reported by Rhett.<sup>161</sup> The drug was administered in doses of 1 gr (0.065 Gm.) per pound (453 Gm) of body weight to a series of 440 children who had symptoms suggestive of poliomyelitis. Only 1 of these children developed paralysis which was mild in character and the symptoms of this patient subsided when the drug was given in greater dosage. Two other children of the group developed meningeal symptoms suggestive of poliomyelitis but paralysis did not occur. Fourteen of the group were thought to have been in the preparalytic stages of the disease but only the 1 child mentioned above developed any transitory paralysis. Eleven other patients with paralytic involvement were treated with neoprontosil and the majority responded rapidly, with the subsidence of their toxic symptoms within 1 or 2 days and a sudden halt of the progress of the paralytic involvement. There were 2 patients in this group with extreme degrees of paralysis which required the use of the respirator to maintain artificial respirations. One of these patients died 2 months later.

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## RESPIRATORY SYSTEM

By WALDO E. NELSON, M.D.

### Stridor

**Etiology**—In view of the frequency with which there is difficulty in determining the cause of respiratory stridor in infancy, it is of interest to note the variety of associated anatomic abnor-

malities observed by Bowman and Jackson.<sup>162</sup> Their series consists of 30 infants with chronic stridor. The investigation of these infants included a roentgenologic examination of the neck and of the chest in both planes and an endo-

scopic examination of the larynx and trachea. There were 14 children with congenital excessive curling and flaccidity of the epiglottis; 5 with enlarged thymus; and 3 with other congenital malformations of the larynx; 1 instance each of a cyst of the thyroglossal duct, tuberculosis of the bronchial lymph-nodes, micrognathia, collapse of part of the trachea, hypertrophic laryngitis, and hypertrophic laryngitis as-

improvement in the stridor, occurring within 48 hours after the roentgenologic treatment, was required.

### Retropharyngeal Abscess

**Complications**—An instance of severe *hemorrhage* secondary to a retropharyngeal abscess is reported by Havens.<sup>163</sup> He points out that, while this complication is rare, it is often fatal, since the hemorrhage is usually

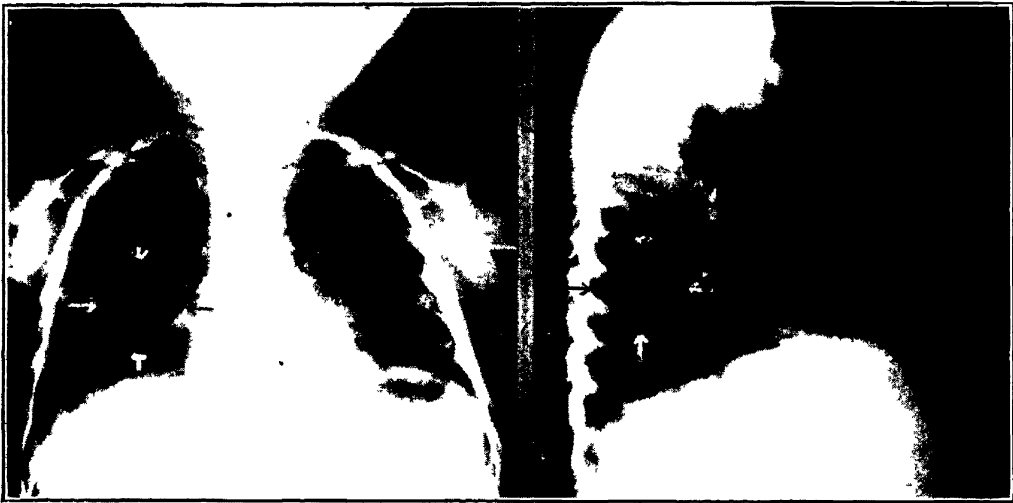


Fig. 8—A, Case 1, Aug. 31, 1932. There is a rounded area of diminished density with a thin dense margin in right lower lung. This does not contain any fluid, and there is very little infiltration in surrounding lung.

B, Direct lateral view showing that area of diminished density is spherical and situated posteriorly in right lower lung (Benjamin and Childe: J. Pediat)

sociated with congenital laryngostridor; and 1 case of undetermined cause. The relative frequency of the finding of an enlarged thymic gland is interesting in view of the current skepticism that an enlarged thymic gland may have anything to do with difficulty in breathing. In these cases the diagnosis depended mainly on the finding on the lateral roentgenogram of kinking, narrowing, and displacement backward of the trachea by a shadow posterior to the manubrium of the sternum. Negative endoscopic examinations were reported in all of these cases. Before classifying a child in this group, however, definite

due to erosion of the carotid artery or one of its large branches. Rapid enlargement of a retropharyngeal mass within a period of a few hours is said to be significant. It may mean erosion of a large vessel even though no blood appears on the surface. If such a condition is suspected, an *aspiration* should precede the *incision*. When there is *bleeding* from, or in association with, a retropharyngeal abscess, the *carotid artery* on the side of occurrence of the abscess should be *ligated* at once. Most patients who require this procedure are young children, and the risk of circulatory cerebral complications secondary

to the ligation is slight compared with the danger of fatal hemorrhage without it.

### Pneumonia

**Complications**—A number of instances of *bullous emphysema* associated with pneumonia in children have been reported by Benjamin and Childe.<sup>164</sup> They suggest that the term "cyst" should not be applied to this lesion and point out that, in contrast, true congenital pulmonary air cyst is a rare condition. All of their cases were associated with pneumonia and frequently with some degree of pleurisy, the latter often being localized in the affected region. There may be an accompanying empyema or, if rupture of the pleura occurs, a pneumothorax. The authors have not observed bullous emphysema in children with pulmonary tuberculosis without pneumonia nor have such lesions been observed by them in the chests of normal children.

The characteristic roentgenologic appearance of localized bullous emphysema described by them consists of 1 or more abnormal areas of diminished density, surrounded by a thin, dense, smooth margin (see Figs. 8 and 9). These may be spheroid or ovoid in shape and may be loculated. These lesions are seen readily when the surrounding lung is comparatively clear; on the other hand, they may be less evident when infiltration is present in the contiguous lung. They become more definite, however, as the density clears. The location of the bullous emphysematous areas is usually subpleural or intrapleural. They may contain some fluid but usually not a great amount. The size varies from very small, when they may be hardly distinguishable, to voluminous, balloon-like spaces, which may occupy a large portion of 1 lung. They usually disappear within a few weeks, but occasionally

months may elapse before the chest returns to normal.

There are no abnormal signs or symptoms unless there is enormous inflation or rupture of the pleura, with formation of a pneumothorax, when there are signs of increased intrathoracic pressure. The *differential diagnosis* between bullous emphysema and lung abscess, localized



Fig. 9—Case 1, Nov. 16, 1934. Follow-up roentgenogram, showing no residual changes at base of right lung (Benjamin and Childe: J. Pediat.)

pneumothorax, congenital pulmonary air cyst, or diaphragmatic hernia is not difficult if the course of the case can be followed for a short time. No treatment is necessary unless complicating conditions ensue.

Similar observations have been made by Caffey.<sup>165</sup> Of the 7 patients who were selected for this report from a larger series of 20, *emphysematous cavities* with shifting air-fluid levels were seen in 4 cases. The benign course of emphysematous cavities is emphasized, since all of these patients recovered without surgical intervention. The question is raised whether air-fluid levels in pulmonary cavities are pathognomonic of pulmonary abscess, and it is suggested

that in these cases inflammatory fluid exudate in emphysematous cavities produce shifting air-filled levels similar to those caused by necrotic fluid in necrotic cavities. An example of benign emphy-

sematous cavities with and without fluid levels is shown in Fig. 10.

**Diagnosis**—A new *suction method* for obtaining sputum from infants and children has been described by Auger.<sup>166</sup>

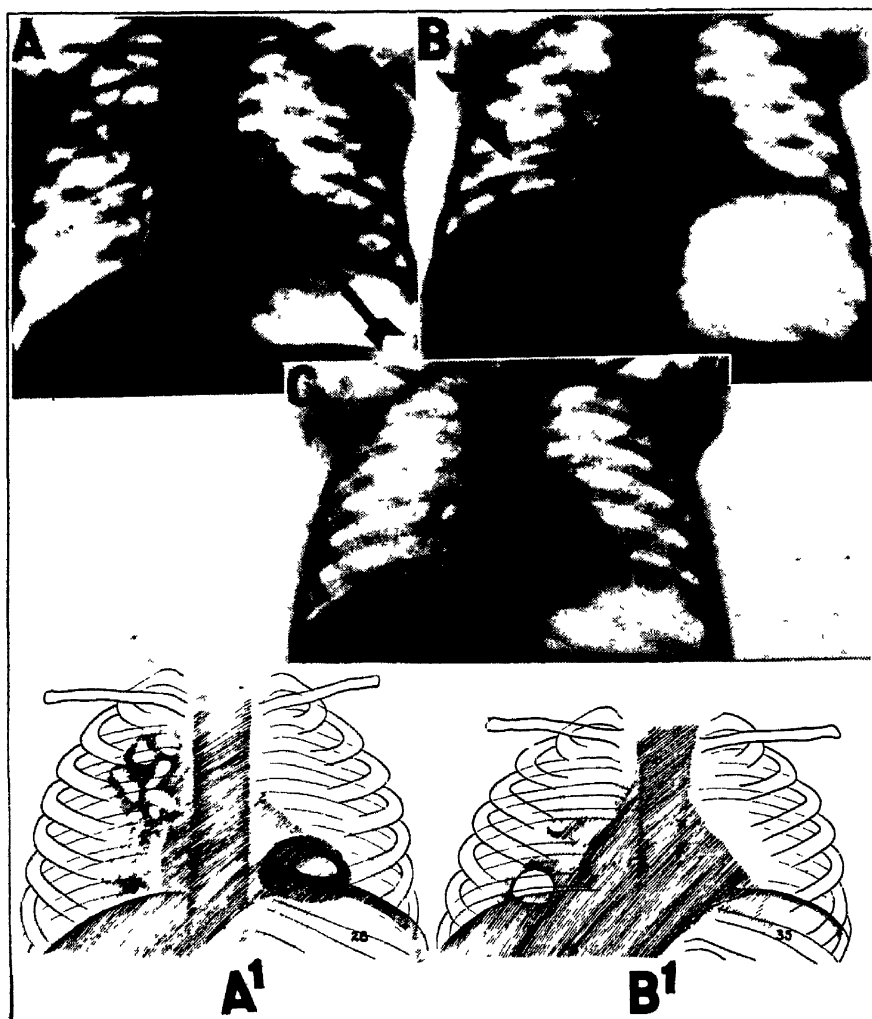


Fig 10—Case 3. Roentgenograms and drawing showing multiple, transient, benign, fluctuating, emphysematous cavities with and without fluid levels. *A*, Roentgenogram made on eighth day of illness, showing large cavity with horizontal fluid level at base of left lung and multiple dry cavities in upper lobe of right lung. *B*, Roentgenogram made on fifteenth day of illness. Large cavity in left lung, as well as some of smaller cavities in upper lobe of right lung, has disappeared. In lower lobe of right lung a new large cavity has developed since examination 7 days previously. *C*, Roentgenogram made 9 weeks after onset of fever. No cavities visible. *A'* and *B'*, Semidiagrammatic representations of *A* and *B* after onset of fever and cough, are shown in *B*, figure 3. Cavity previously present in left lung had practically disappeared, while a new cavity, 20 by 15 mm., was present in lower lobe of right lung. In upper lobe of right lung the multiple small cavities were reduced in number and had changed their pattern. *C* shows disappearance of all pulmonary lesions at time of discharge from hospital, 9 weeks after onset of cough and fever.

Bronchoscopy repeated 3 weeks after onset of fever, and amount of purulent exudate visible in bronchial tree was much reduced as compared with first bronchoscopic examination 2 weeks before. Septic fever persisted for 3 weeks after onset, when it subsided and physical signs in chest disappeared. Patient remained in hospital for 6 additional weeks, and there was no recurrence of symptoms indicative of relapse in the pulmonary infection. Mastoidectomy wounds healed satisfactorily. Patient has been under observation for 9 years, and lungs have appeared normal in repeated clinical and roentgenographic examinations. (Caffey. *Am. J. Dis. Child.*)

By this method the author claims to be able on the first attempt to obtain sufficient sputum from either the larynx or the nasopharynx to carry out an examination by direct smear and by typing according to the Neufeld method. The *laryngeal method* is recommended in cases of suspected tuberculosis, whooping cough, or pneumonia due to mixed infection, while sputum from the nasopharynx is ideal for typing pneumococci.

The method is based on aspirating sputum from the throat while the child coughs. The apparatus consists of an ordinary glass 50 cc syringe, a 2-inch piece of soft rubber tubing of  $\frac{3}{16}$  inch inside diameter with a small hole cut in 1 side (so that the thumb can easily cover the hole and thus act as a valve), a 2-inch piece of glass tubing of  $\frac{1}{4}$  inch outside diameter, and a 3-inch to 4-inch piece of slightly curved stiff rubber tubing or a catheter of  $\frac{1}{8}$  inch inside diameter with a notch cut in either side of the tip. The piece of soft rubber tubing is clipped over the tip

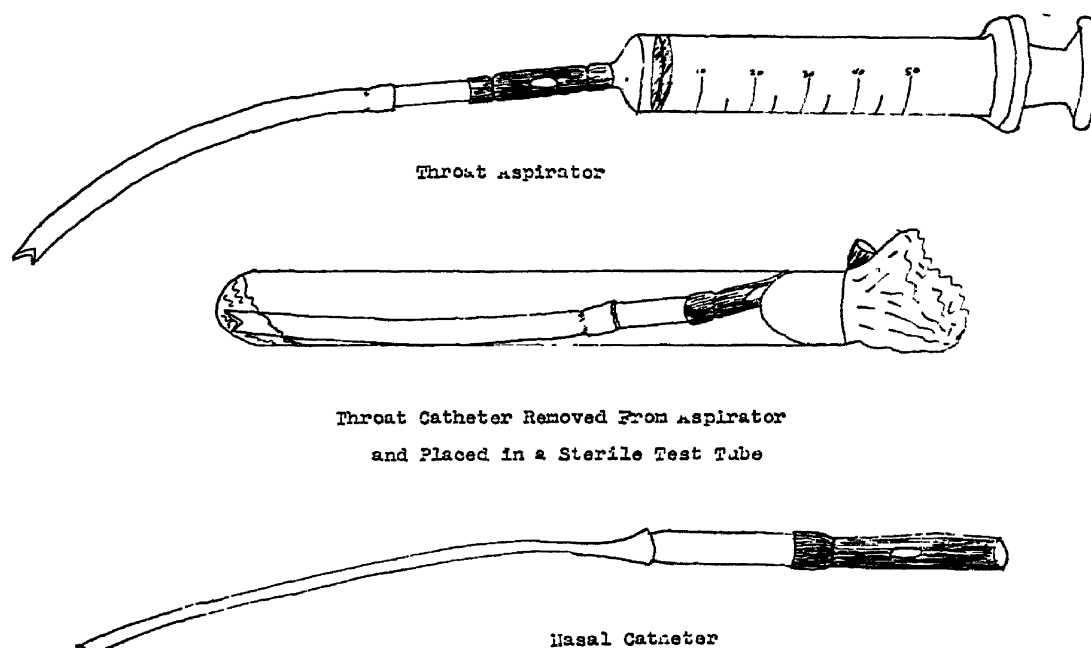


Fig 11—Diagram of apparatus. (Auger · J. Pediat.)

The nasopharynx is described as a breeding ground for pneumococci and as the probable route by which pneumococci reach the lung in pneumonia of infants and children. The author has found that the nasopharyngeal method of sputum examination is invaluable in the diagnosis of obscure febrile conditions, particularly in the differential diagnosis between pneumonia and *acute appendicitis*; it is inferred that when large numbers of pneumococci are found in the nasopharynx before any physical sign in the chest can be recognized, the child is developing pneumonia and does not have an acute appendicitis.

of the syringe and is connected to the catheter with the short glass tube. The apparatus when assembled and boiled is ready for use (see Fig. 11). A nurse stands at the head of the bed holding the arms of the child firmly above his head, and the operator stands at the patient's right. The barrel of the syringe is held in the left hand, with the thumb covering the hole of the valve. The right hand first holds the end of the catheter which is quickly inserted toward the uvula until the child gags or coughs and opens his mouth widely. The right hand then changes position, grasping the handle of the piston, and suction is commenced with the tip of the catheter as close to the larynx as possible. Suction is performed by pulling the piston out with the right hand and with the left thumb at the same time covering the hole in the soft rubber

tube or valve. At the end of the upstroke, the thumb is removed from the hole, and the piston is shoved back into the barrel. In this manner the sputum is not returned into the throat by the instroke of the plunger; and by fast, repeated in- and out-strokes of the plunger, co-ordinated with the removal of the thumb on every in-stroke, a powerful intermittent suction is obtained. This strong suction in the back of the throat serves to aspirate the sputum from the larynx and to irritate the cough reflex, thus making the cough more explosive. The whole procedure should be done quickly and energetically, since the child is unable to breathe properly during the operation.

Slightly different equipment is necessary for *nasopharyngeal suction*. The stiff rubber throat catheter is replaced by a 7-inch rubber tube, the diameter of which depends on the child's nares; in general, a No. 9 French catheter is suited to infants up to the age of 6 months, and a No. 10 is satisfactory for children over this age. The nasal catheter is passed through the nares until it is judged to have reached the adenoid area. Suction is then commenced and is continued while the catheter is slowly withdrawn from the nose. The child does not need to cough. The sputum is then forced out of the catheter into a sterile culture tube. Having transferred the sputum to the culture tube, the tube is removed from the syringe, and the catheter and tube are left in the culture tube. In the laboratory saline is added to the sputum in the culture tube, and the contents of the culture tube are then emptied into a Petri dish for examination.

#### Treatment — Serum Therapy—

Good results in the treatment of pneumococcic pneumonia Type XIV in children with specific serum is reported by Bullowa and Gleich.<sup>167</sup> Pneumococcus Type XIV is said to be the organism most frequently found in very young children with pneumonia. The mortality is higher before the age of 3 years. In the authors' experience, when specific serum is employed in adequate amounts, the mortality even in the presence of bacteriemia is reduced, the disease is shortened, and complications are fewer. Of interest in this respect is the discus-

sion by Blackfan of a paper by Christian, Jorgensen, and Ellis.<sup>168</sup> Attention is called to a case in which the pneumonia was due to Type XIV pneumococcus and in which *sulfapyridine* did not appear to be effective until after the administration of *antipneumococcic serum*.

*Sulfathiazol*—In the experience of Scott and Jones<sup>169</sup> sulfathiazol is as efficacious as sulfapyridine in the treatment of pneumonia in infants and children. They have treated 167 cases of pneumonia in infants and children with sulfathiazol and have compared the results with a previous series treated with sulfapyridine. Of those treated with sulfathiazol, 5 died, all of them being under 1 year of age. Seven of the patients developed pleural effusions. In one of these cases sulfathiazol was ineffective and sulfapyridine was used with success. In their estimation sulfathiazol is as effective as sulfapyridine in producing a critical fall in temperature. Perhaps the most significant difference is the fact that there were less toxic effects with sulfathiazol than with sulfapyridine. The toxic effects from sulfathiazol were largely gastroenteric, consisting of vomiting and diarrhea. The dosage of sulfathiazol employed was 1 grain (0.06 Gm.) per pound (453 Gm.) of body weight. Usually one-fourth to one-half of this amount was given as an initial dose, and then one-eighth of the dose was given every 3 hours day and night, the patients being awakened if necessary. This was continued until the temperature had been normal for 48 hours or until it was felt that the drug was no longer necessary.

Twenty-one cases of lobar pneumonia treated with sulfathiazol have been studied by Y. Kneeland, Jr., and B. Mulliken<sup>170</sup> for the appearance of an excess of type-specific antibody in the blood serum by means of the precipitin reac-



tion with specific polysaccharide. Sixteen of these had an excess of antibodies at the time the temperature became normal, or thereafter. Since they had previously observed that about three-fourths of the patients treated with sulfapyridine did not show antibodies, they concluded that there appeared to exist a greater stimulation of this immune

his observation of the Schilling blood count in children with lobar pneumonia treated with sulfapyridine. He points out that there is a constant relation between a natural crisis and the decrease in the nonfilamented polymorphonuclear leukocytes of the blood in lobar pneumonia which does not appear in the artificial crisis induced by sulfapyridine.

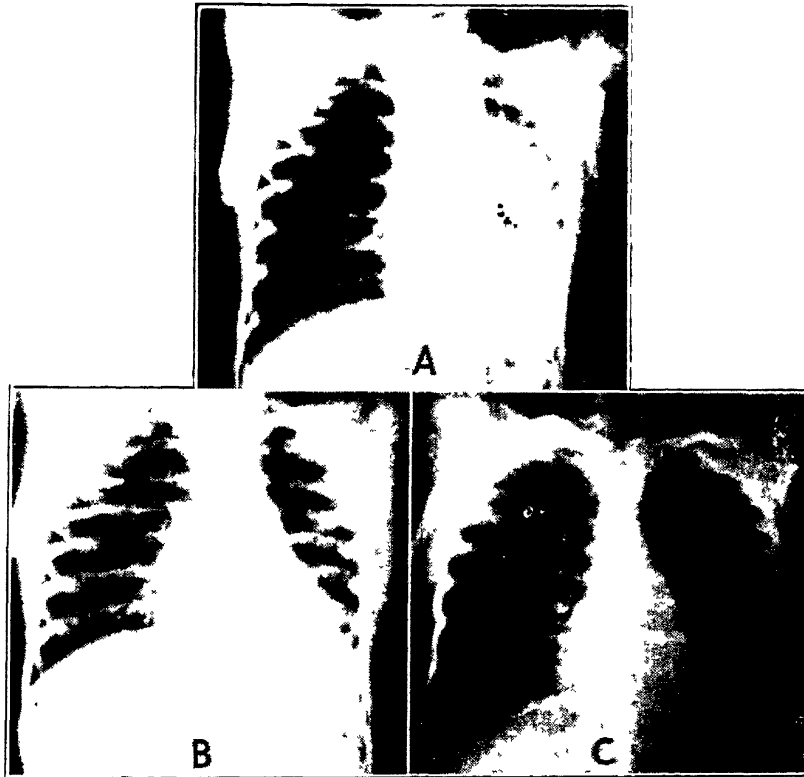


Fig 12—Case 1. Roentgenograms taken: *A*, on patient's admission to hospital, *B*, 3 days after bronchoscopy, *C*, 1 month later. (Friedman and Molony · *Am J. Dis. Child*)

mechanism in patients treated with sulfathiazol than in those treated with sulfapyridine. This they interpreted as indicating that sulfapyridine is a somewhat more powerful antipneumococcal agent than sulfathiazol.

**Sulfapyridine**—Rogatz<sup>171</sup> does not agree with those who believe that in addition to the interruption of the typical clinical course of lobar pneumonia by the administration of sulfapyridine there is also hastened resolution of the pneumonic process. This is based upon

His studies suggest that the pathologic course of lobar pneumonia is not greatly altered by the administration of sulfapyridine and that, despite the obvious clinical improvement and the fall in temperature, the immature granulocytes of the blood do not reflect this improvement but rather indicate a continuation of the familiar process of hepatization and resolution which characterizes the course of the untreated patient. In view of these observations the author emphasizes the importance of continuing con-

valescence, as with the untreated patient, at least until the blood smear has returned to normal.

### Allergic Atelectasis

Six cases of nontraumatic, nonpost-operative atelectasis, and 1 case of post-operative atelectasis occurring in allergic children have been reported by Friedman and Molony.<sup>172</sup> The processes in bronchial asthma which may produce bronchial occlusion are bronchospasm, thickening of the bronchial walls, secretion of thick mucus, and paradoxical collapse of the bronchi during expiration. It appears that bronchial occlusion is the principal cause of atelectasis.

The *treatment* of atelectasis must be directed first toward the immediate relief of the patient and secondly toward methods of preventing recurrence. The

first step consists in removing the mucous plug from the bronchus. The ordinary indirect methods are *postural drainage* and the use of *expectorants* and *drugs* which increase the bronchial secretion or render it more liquid. *Epinephrine hydrochloride* administered subcutaneously makes the patient more comfortable but does not aid in dislodging the tenacious mucoid plug. If the condition persists, the authors believe that *bronchoscopic aspiration* is the method of choice and should be repeated when necessary. The subsequent care of the child should include a thorough allergic study and the elimination, if possible, of the exciting factor. The possibility of recurrent atelectasis as a precursor of bronchiectasis is suggested. An illustrative case is shown in Fig. 12 on the preceding page.

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## SCARLET FEVER

By ROBERT A. LYON, M.D.

**Complications**—*Liver damage* and its relationship to the *nephritis* of scarlet fever has been studied by Carslaw.<sup>173</sup> He noted that the amount of urea excreted in the urine of scarlet fever patients gradually diminished during the course of the disease, with minimum amounts excreted at the end of the third week. In the patients who developed nephritis, the quantities were generally lower than in those who recovered without this complication. Since urea is formed almost exclusively in the liver, it seemed probable that hepatic disturbance was a frequent occurrence in scarlet fever and that its insufficiency was related to the development of nephritis.

**Treatment** — Concentrated scarlet fever *antitoxin* has been employed successfully in the passive immunization of

children by Bradshaw.<sup>174</sup> A group of 658 children received 0.75 cc. of the serum routinely on admission to the hospital and only 1 developed scarlet fever. In another group of 135 susceptible children directly exposed to a patient with scarlet fever on the wards, all received similar treatment and all escaped the disease. Serum reactions occurred in 1.2 per cent of cases.

A purified antitoxin of low protein content has given good results in the scarlet fever patients treated by J. A. Toomey and E. R. Kimball, Jr.<sup>175</sup> Doses of 6000 units which were administered to 500 patients led to a rapid disappearance of the rash within 12 to 14 hours and a diminution in the severity of the complications. The mortality rate of the entire series was 1.6 per cent.

Local and systemic reactions to the purified antitoxin were much less frequent than those noted in previous series of patients who had received other types of the antitoxin.

The antitoxin and the antibacterial content of scarlet fever *convalescent serum* has been examined by Moore and Thalhimer.<sup>176</sup> The titers of antitoxin in 51 samples of convalescent serum ranged from less than 1 unit to 10 units per cubic centimeter, with average values of 3.3 units. A gradual diminution of the antitoxin content occurred during the period of 6 months after the onset of the disease. The antibacterial properties of convalescent serum were tested with 4 different strains of the streptococcus. None of the serums were able to kill bacteria of all 4 types, but 8 specimens were effective against 2 types and 9 had no effect upon any type. None of the serum samples contained bacterial antigens capable of combating more than 1 virulent strain of streptococcus. In some sera the bactericidal powers remained for several months but in others there was absence of the substance 6 months after the onset of the disease. These findings indicated the necessity of pooling sera in order to obtain antitoxin and antibacterial properties suitable for combating all types of illness. Sera from patients convalescent from recent infections would be most effective.

Favorable results from the use of *sulfanilamide* in the treatment of patients with scarlet fever have been reported by Benn.<sup>177</sup> A series of 253 children under 10 years of age received the drug for 1 week and alternating patients were left untreated. Complications occurred in only 15 per cent of the treated group as compared with 25.3 per cent of the group untreated. Rheumatism, endocarditis

and myocarditis were entirely absent in the treated group but did occur in the control series. By administering the drug for 2 weeks and again during the fourth week of the disease, in another series of patients, the incidence of complications was reduced to 11.4 per cent.

No benefit from the use of sulfanilamide in the treatment of scarlet fever patients could be detected by French.<sup>178</sup> Of a series of 340 patients admitted to the hospital, every other one received the drug for a period of 14 days. The treated and the untreated groups were comparable in age, severity of infection, and stage at which the drug was started. The sulfanilamide had no effect in shortening the course of the initial fever or the rash. Complications occurred with equal frequency in the treated and untreated groups and the single death of the entire series took place in a treated patient. The drug produced cyanosis in 10 per cent of the patients, rashes in 11.5 per cent, anemia in 1 and possibly may have caused nephritis in another patient. The large number of reactions caused by sulfanilamide and its failure in reducing the incidence of complications led the author to conclude that it should not be employed in the treatment of scarlet fever.

The *effect of sulfanilamide upon the blood cells* of patients with scarlet fever was limited chiefly to the depression of the number of polymorphonuclear leukocytes. French<sup>179</sup> found that the greatest decrease occurred during the first week of the disease and a less marked diminution in later stages. Never did a leukopenia occur but the author believes that the development of an agranulocytosis should be watched for during the period of medication.

## SMALLPOX

By ROBERT A. LYON, M D.

**Vaccination**—The results of *intra-dermal vaccination* of newborn infants, compared with those of the *cutaneous method*, have been recorded by Donnally, Nicholson, Anderson and Grosvenor.<sup>180</sup> A successful take by the intracutaneous inoculation method was determined by the definite vaccinal cycle which it followed rather than by the size of the reaction. The course was very similar to that of a cutaneous inoculation. Undiluted calf lymph virus and that which had been diluted 1:100 were used for the intradermal inoculation. The incidence of takes in these 2 groups was about 93 per cent with either method. When culture virus was used, the incidence of takes dropped to 80 per cent. Cutaneous vaccination employing undiluted calf lymph caused severe reactions in about 10 per cent of the newborn. The intradermal vaccination with calf lymph diluted 1:100, however, caused very few reactions and yet the degree of success by the use of this procedure was just as great as with the cutaneous method. Reactions to the intradermal vaccination method consisted chiefly of lymph adenopathy but the cutaneous reaction was minimal and bacterial infection was entirely absent. The routine vaccination of the newborn in hospitals would reach a large number of patients who might not seek the advice of physicians during the early years of life.

*Tests of the immunity* conferred on newborn infants by various methods of vaccination have been made by Donnally.<sup>181</sup> Seventy children who had been vaccinated during the early days of life were revaccinated 3 years later. Thirty-six of this group had had primary takes at birth with *culture vaccine virus* in-

oculated intradermally. The remaining children had been vaccinated with *calf lymph virus*, some intradermally and the others by the cutaneous method. Two or 3 years later vaccinations were performed with a fresh lot of calf lymph virus inoculated by the multiple pressure method and the reactions of 18 of the group were followed carefully throughout the succeeding days. The degree of their immunity was judged by the type of the reaction. About 81 per cent of the infants who had been primarily vaccinated with the culture virus were found to have slight or no immunity at this time, while only 21 per cent of the children who had had primary vaccinations of calf lymph showed slight or no immunity. Good immunity was found in only 5.5 per cent of those who had been vaccinated with culture virus and in 73.5 per cent in those who had been inoculated with calf lymph. These results seemed to show that the culture virus had many advantages in ease of preparation and transportation and in freedom from contamination by bacteria and other viruses, but was not as effective an agent in producing lasting immunity as the calf lymph. It has been shown, however, that the culture virus vaccinations will check the spread of smallpox. The vaccination of newborn infants is successful in high percentages of cases by either the intradermal or the cutaneous inoculation and this immunity is lasting when calf lymph is employed.

The presence of a *specific antibody in convalescent serum* obtained from recently vaccinated patients has been demonstrated by Greengard and Wolf.<sup>182</sup> They collected serum from donors who had been vaccinated 17 to 24 days previously,

and injected doses of 10 to 20 cc of it into infants 3½ to 10 months of age. Twenty-four hours later these children were vaccinated with smallpox virus and another group of the same age which did not receive the serum served as a control

series. The number of takes in the treated group was only slightly more than one-half that of the control infants, which led the authors to conclude that the convalescent serum contained a specific protective material.

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## CONGENITAL SYPHILIS

By ROBERT A. LYON, M.D.

**Incidence**—The incidence of syphilis in a children's clinic was found to be 0.48 per cent by Clifton and Heinz.<sup>183</sup> A total number of 5,625 patients who were admitted to the clinic during a period of 1 year were tested with various types of serologic reactions. Only a small percentage of the total number of patients were negroes but the incidence of congenital syphilis in this group was much higher than in the white children. This incidence of syphilis in the entire clinic was much lower than has been reported previously from other localities. During the period of time there were 82 patients who had false positive or doubtful reactions, possibly due to other infections or febrile reactions of the patient. These children had such diseases as upper respiratory infections, skin eruptions, pneumonia, pertussis, pylorospasm, scurvy and other diseases. The *Kahn test* proved to be the most sensitive test but it tended occasionally to give false positive reactions in the group of children who were sick with other diseases. The *Wassermann reaction* gave no such false positive results, so the authors concluded that in doubtful cases both of these types of tests should be used before a definite diagnosis was made. Of the 27 instances of true syphilis, 1 had acquired the disease through a blood transfusion, and 22 of the re-

maining 26 patients had other symptoms and signs suggestive of the disease.

**Intelligence Quotient**—The intelligence of syphilitic children has been determined by H. H. Perlman and M. W. Gardiner.<sup>184</sup> A total number of 50 children, the majority of whom were between 5 and 12 years of age, were given intelligence tests. The average intelligence quotient for the group was 90.3. There were 6 children with the intelligence quotients above 110 and 6 were below 70. The distribution was normal for any group of this age and type of population. One child, who had a strongly positive Wassermann reaction of the cerebrospinal fluid, was in the imbecile class. In the absence, however, of any central nervous system involvement, syphilis did not seem to have any effect upon the mentality of the patients.

**Diagnosis**—The difficulties in making an accurate roentgenologic diagnosis of syphilis in infants during the first few weeks of life have been enumerated by Christie.<sup>185</sup> In only 2 patients of a group of 83 infants born of syphilitic mothers could the diagnosis of syphilis be made accurately by roentgenograms of the long bones. In 47 infants the absence of syphilis was correctly interpreted, and in 23 others, a doubtful diagnosis was made, but 3 of these later developed other evidence of syphilis and 20 did not. In a group of infants whose

mothers had received bismuth injections during pregnancy for the treatment of their syphilis, the roentgenograms showed transverse bands of increased density separated by zones of rarefaction. Lesions which have usually been interpreted as indicative of syphilis, such

seem advisable to delay the diagnosis and treatment until positive serologic reactions or other proof of syphilis can be obtained.

The possibility that many other conditions than syphilis might cause the lesions typical of that disease has been

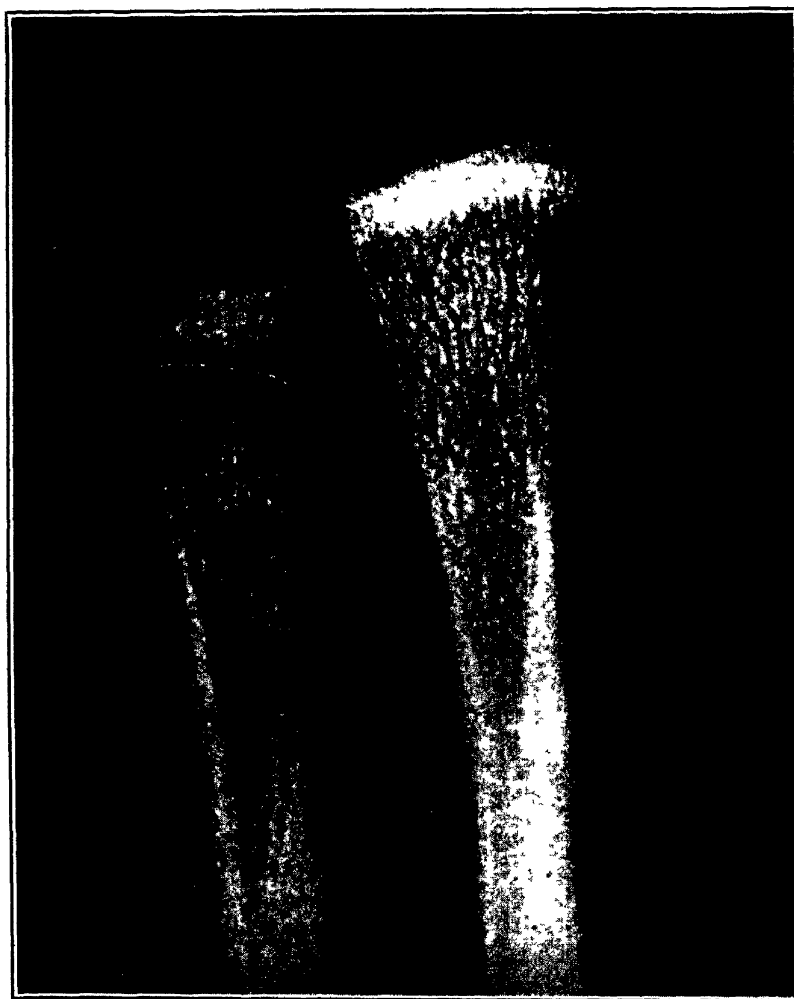


Fig. 13—Lower end of radius and ulna of infant whose mother had received 7 weekly injections of bismuth, showing transverse areas of increased density (Whitridge: Am. J. Syph., Gon. and Ven. Dis.)

as areas of rarefaction of the submetaphyseal zone and subcortical and fine periosteal shadows, were observed by the author in nonsyphilitic infants who had been growing rapidly. If other conditions can produce roentgenologic changes resembling those of syphilis in the long bones of young infants, it would

emphasized also in the study of Caffey.<sup>186</sup> In series of 22 cases reported there were many lesions which resembled the osteochondritis, periostitis or the osteomyelitis of syphilis but were in reality caused by other diseases. In 14 instances an *osteochondritis* was due to a bacteremia of staphylococcus, pneu-

nococcus or the tubercle bacillus. Such conditions as *erythroblastosis fetalis*, *hemolytic anemia*, *birth injuries*, *congenital atresia of the bile duct*, *malnutrition*, types of *encephalitis* and *maternal bismuth treatment* caused bone lesions simulating those of syphilis. *Periostitis* simulating that of syphilis was observed in nonsyphilitic infants who were suffering from healing rickets, traumatic lesions, gonorrheal bacteremia, and nutritional disorders. *Osteomyelitis*, typical in syphilis, was noted in nonsyphilitic infants who had pyogenic osteomyelitis. It was the conclusion of the author that in childhood, syphilitic bone lesions may be simulated by many other conditions, and that the roentgenologic changes were not conclusive evidence of syphilis. When all 3 types of lesions, the osteochondritis, periostitis, and osteomyelitis, were present in combinations, the diagnosis of syphilis was more certain. The author quoted the statement of Wimberger that if it is impossible to detect syphilis by other methods, the roentgenologic findings, as a rule, will not make the diagnosis.

Although it had been demonstrated previously that the administration of *bismuth to syphilitic women during pregnancy caused the deposition of the metal in the long bones of infants*, it was never certain whether these changes might not have been due to syphilis itself. J. Whitridge, Jr.,<sup>187</sup> has administered 16 minims (1.0 cc.) of bismuth salicylate in oil for about 8 weeks to 12 nonsyphilitic mothers during the last trimester of pregnancy. Nine of the infants had roentgenologic evidence of deposition of the bismuth in the long bones, the changes consisting of transverse white lines of increased density near the end of the shaft (Fig. 13). The alteration of the bony structure seemed to be independent of the amount of bismuth the mothers received.

**Treatment**—In a comparison of the results obtained with *acetarsone* administered by mouth and of the *neoarsphenamine* or other arsenicals administered intravenously or intramuscularly, Lyon and O'Neil<sup>188</sup> found that the oral medication was satisfactory. In a group of 15 infants less than 2 years of age treated with acetarsone negative serologic reactions and the absence of symptoms or signs of syphilis occurred in 67 per cent. In the group of 19 infants of the same age who received other arsenicals they obtained equally good results. Among older children there were 38 children treated with acetarsone and 62 treated by other arsenicals. Good results were obtained in 34 per cent of those receiving the oral treatment and in about 21 per cent of those receiving the other arsenicals. As a rule, the children whose treatment was instituted before they had reached the age of 2 years responded much better to either type of therapy than the children of older age levels. Variations between the effectiveness of the types of arsenicals used were not great and were not of statistical significance.

The results of the treatment of congenital syphilis with *mapharsen* have been recorded by Howles.<sup>189</sup> Mapharsen was administered intravenously alone to 59 patients, and in conjunction with bismuth in 145. *Sulpharsphenamine and mercury inunctions* were used in 46 patients who served as a control group. Reactions to the mapharsen were very few in number and very little local tissue inflammation was caused by the material when it was given subcutaneously and intravenously. The combination of *mapharsen with bismuth* seemed to give the best results. Of the children between the ages of 1 and 3 years treated with mapharsen only, 62 per cent became serologically negative and those of

older ages had reversals in 50 to 60 per cent of instances. In the infant group in which *bismuth salicylate therapy* was added, the percentage of serological reversals was 71 and in older age groups from 52 to 65. This compared favorably with the use of sulfarsphenamine in 46 children under 1 year of age.

A new chemical compound called *trisodium arsphenamine sulfonate*, or *trisodarsen*, has been employed in the treatment of congenital syphilis by Givan and Villa.<sup>190</sup> This compound is a yellowish powder readily soluble in water and its arsenic content was not less than 19 per cent. It has a low toxicity for experimental animals. The group studied included 147 patients varying in age from 8 days to 50 years, the majority of whom were children under 16 years of age. The dosage of the drug varied from  $\frac{1}{12}$  to  $1\frac{1}{2}$  grains to 11 grains (0.005 to 0.1 Gm. to 0.7 Gm.), according to the age of the patient, and it was usually administered intravenously, although it can also be employed intramuscularly without danger. Injections were given at weekly intervals. Local reactions were very slight when the material was given intramuscularly or into the subcutaneous tissues. Forty of the group had mild systemic reactions of nausea, vomiting or mild skin eruptions; 1 had a severe reaction consisting of dermatitis exfoliativa, and 1 patient had a nitritoid reaction. The drug seemed effective in the improvement of interstitial keratitis, skin eruptions, snuffles, and bone and joint lesions of syphilis. Of 121 patients who had positive Wassermann reactions before the treatment was started, 76 per cent became negative. Of a group of 69 patients who had examinations of the spinal fluid, all except 4 had negative tests by the end of the treatment. Two patients with

positive cerebrospinal fluid findings were not improved by the therapy.

The importance of prevention of congenital syphilis by the adequate *treatment of the infected mother during her pregnancy* is well known. If this is impossible, the *early treatment of the syphilitic infant* is the next most important method of completely curing the illness. The difficulties in carrying out either program adequately have been emphasized by Lyon and Seymour.<sup>191</sup> Among a group of 187 syphilitic mothers, only 25 were found to have received any antisyphilitic treatment and only 6 of this group, or 3 per cent, had had an adequate amount of antisyphilitic treatment during their pregnancy. After the children were born, approximately 39 per cent of the mothers failed to return to clinics for treatment of their infants, in spite of the fact that they had been told of the necessity of the visits and appointments had been made for their care. Experience has shown that if the infant is not treated in the early months of life he may be lost from supervision, and the detection of syphilis may be delayed until definite symptoms develop or routine blood tests happen to be made in hospitals or clinics in later years. The failure of at least one-half of the total number of children with syphilis to develop definite symptoms in the early years of life may also postpone the diagnosis of the disease until late childhood.

In order that the infants whose mothers had positive serologic tests should not escape treatment, the authors instituted treatment of 36 infants immediately after birth without waiting until an absolute diagnosis of the disease could be made. These 36 infants were treated with *acetarsone* and with *mercury rubs* for a period of 1 year. At the end of that time all of the group had been free from symptoms and had



negative serologic reactions except 1 patient whose treatment had been interrupted and was not instituted continuously until several months after birth. Ten of the group had been observed for 1 to 3 years after the termination of the treatment and all of these had remained free from symptoms of syphilis and had

negative serologic reactions. It was the conclusion of the authors that the early treatment of the disease was a most important factor of antisyphilitic therapy. The routine treatment of infants of syphilitic mothers who had not had adequate therapy during their pregnancies seemed to be a logical procedure.

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## TETANUS

By WALDO E. NELSON, M.D.

**Treatment**—Dietrich<sup>192</sup> has analyzed the treatment of tetanus in 28 children in his hospital during the past 19 years. He states that the initial administration of *tetanus antitoxin* by vein or into the subarachnoid space was always followed by a severe and often by a fatal *reaction*. The reaction was characterized clinically by extreme hyperthermia, marked tachycardia, coma, irregular respirations and, in some instances, sudden death. Death occurred within 36 hours, and in 84 per cent of the cases it occurred within 3 to 14 hours after the first treatment. Pathologically, medullary and general cerebral edema were found. The only 4 patients in the entire series who did not show untoward reactions to serum therapy received serum only intramuscularly; these patients made an uneventful recovery. During the years 1921 to 1932, 12 of 15 children with tetanus died; from 1932 to 1939, 1 of 13 cases died. From a review of the case records it appeared that most, if not all, of the deaths in the first group and the only death in the second group occurred as a direct result of treatment. It was thought that the improved rate of mortality in the second group was due to the more judicious and less enthusiastic use of serum and to an increasing dependence upon sedatives. The refinement of

serums in recent years may have been a factor in reducing the number of severe reactions. Severe serum reactions, however, did occur in some of the children who survived.

The author states that 1500 units of tetanus antitoxin is not adequate prophylaxis in cases with compound fractures. On the other hand, moderate doses of serum are thought to be theoretically adequate for treatment. Intrathecal administration of serum is condemned as being dangerous. Although intravenous administration of serum may be the cause of a fatal reaction, the author advises an initial intravenous administration in severe cases. Intramuscular injection of serum provides a slower and more continuous source of antitoxin and by itself is adequate, except possibly in the most severe cases. The author also advises the administration of 10,000 to 20,000 units per day for 2 to 4 days to neutralize any new toxin liberated.

In many instances the author observed definite *compression deformities of the dorsal vertebrae*. Pain and tenderness over the affected region are the early manifestations. No symptoms occurred in many cases of this series, and the complication was discovered only because roentgenograms were taken of the dorsal vertebrae in all cases of tetanus.

It is said that pain or kyphosis may appear months or even years later. The orthopedic treatment, including employment of *hyperextension* and the wearing of *jackets* during the patient's convalescence, apparently prevented any serious permanent deformity. Because the lesion is due to the severe tonic muscular contractions, the author suggests the possibility that a more uniform and a smooth sedation may prevent the complication.

An analysis of 2 different plans of treatment of tetanus has also been made by Spaeth.<sup>193</sup> Prior to June, 1933, the patients with tetanus had been given general ward care, antitoxin in repeated doses intrathecally as well as by other routes, radical surgical care of the local lesions, and variable amounts of sedation. Since the above date the patients have received systematic sedation with *avertin*, *amylene hydrate*, and/or *sodium amytal*, a single intravenous or intramuscular injection of 10,000 to 82,000 units of *antitoxin*, *conservative surgical therapy* and *careful general management*, with the emphasis on constant nursing care, prevention of pneumonia, and maintenance of an adequate fluid and caloric intake. Although the total decrease in mortality rate was only 9 per cent with the newer routine, there was greater reduction in mortality in the more recent series when only the severe cases were considered.

On the basis of titration studies and clinical observations, a routine dose of 60,000 units of *antitoxin* is proposed for patients admitted for treatment during the first 5 days of the disease, and a dose of 40,000 units for mildly and moderately ill patients who receive their first treatment at a later date. The intrathecal administration of antitoxin is condemned. In the opinion of the author, surgical treatment is not an emergency procedure and is secondary in importance. Radical operation is justified only when a structure is already hopelessly destroyed. Treatment of wounds with oxidizing or other solutions may facilitate drainage and healing but cannot destroy the tetanus bacilli. All measures, specific and symptomatic, ordinarily employed in the treatment of pneumonia should be instituted when this complication occurs.

Tetanus may occur despite local surgical care, the application of antiseptic agents, or the prompt injection of specific antitoxin in the doses ordinarily recommended. Depending on the circumstances, it is suggested that the prophylactic dose of *antitoxin* may be increased to 5,000, or even to 20,000 units. In view of the numerous insurmountable difficulties encountered in the *prophylaxis* of this disease, active immunization with *tetanus toxoid* is recommended for routine use.

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## TUBERCULOSIS IN INFANTS AND CHILDREN

By WALDO E. NELSON, M.D.

**Pathology**—The incidence and significance of small *calcified spherical bodies in the liver, spleen, and kidneys* have been studied by Reichla and Work.<sup>194</sup> The occurrence of these

bodies in the liver, spleen, and other of the parenchymatous viscera is well known to pathologists and to roentgenologists. Little attention, however, has been given to them. From time to time

they have been referred to as healed "hematogenous tubercles," but more commonly they have been called "phleboliths." The authors found such bodies in approximately one-fifth of the bodies coming to autopsy at the City Hospital, Cleveland. Many, if not all, of the small spherical bodies found in the liver, spleen, and kidneys were true miliary tubercles. They were histologically indistinguishable from small primary tubercles. Animal inoculation demonstrated the presence of tubercle bacilli. The authors argue that the distribution of these bodies points to hematogenous dissemination and that their morphology is associated in point of time with the primary complex. It is postulated that the high correlation between the apparent resistance to progressive tuberculous disease and the incidence of these lesions suggests that this dissemination acts as autovaccination, conferring a relatively high degree of immunity.

**Diagnosis — Basal Metabolism—** Further studies on the basal metabolism of tuberculous children have been made by Topper and Shore.<sup>195</sup> Records were made of the physical signs, roentgen findings, sedimentation rates, blood counts, and basal metabolic rates on children with active afebrile pulmonary tuberculosis of the primary type. From these observations it was noted that children with active afebrile primary tuberculosis had increased basal metabolic rates as long as there were signs of activity. When the tuberculous process became inactive, as evidenced by absence of physical signs, negative x-ray findings, and a normal sedimentation rate, the basal metabolism returned to a normal level. The authors believe that the basal metabolic rate is of diagnostic value in determining whether a primary lesion is active or inactive. This does not apply to the adult type of tuberculo-

sis, in which the rate remains normal even in the presence of extensive active pulmonary lesions.

In a subsequent study Topper<sup>196</sup> observed that the basal metabolism of afebrile children with tuberculosis of the bone was not increased. Of the 14 children who had increased basal metabolism, 12 had an active primary pulmonary lesion in addition to the tuberculous lesion of the bone. From this additional evidence the author concludes that when an afebrile child with a tuberculous bone lesion is found to have increased basal metabolism, the presence of an active primary pulmonary lesion should be suspected.

**Tuberculin Test—**A number of studies designed to test the relative efficiency of the *intradermal tuberculin test* and of the *Vollmer patch test* have been carried out during the past year. Only 2 of them will be cited here. Pearse, Fried and Glover<sup>197</sup> found the 2 tests to be essentially equal in their ability to elicit skin reactions. Of 712 children, who received the patch test and the intradermal test with the first and the second strengths of PPD, a total of 616 had either both tests positive or both tests negative. There were 67 positive patch tests associated with negative intradermal tests in contrast to 21 positive intradermal tests in association with negative patch tests. They conclude that the 2 tests have a high degree of correlation and, because of the objections to intradermal testing, recommend the patch test for large scale tuberculin surveys.

Comparative observations between the Vollmer patch test and the intracutaneous test with PPD, in which the results are not as satisfactory with the patch test are reported by Peck and Wegman.<sup>198</sup> Tuberculin tests by the intracutaneous method and with the patch test were performed on 880 children. The patch test

was found to be positive in only 30 per cent of the cases which were positive either to the first or to the second testing strength of PPD.

In recent years there have been several reports indicating that the *tuberculin test* may be negative in association with healed or calcified tuberculous lesions. As a consequence of these observations, there is in some quarters a skepticism concerning the value of tuberculin as a case finding method. So far evidence has not been presented indicating that anergy to tuberculin exists in association with active tuberculous lesions except in the terminal stages of the disease. A recent survey by Douglas<sup>199</sup> provides further evidence that the correlation between reaction to tuberculin and active tuberculous disease is of a high order. In this series the tuberculin test was negative in only 8 out of 500 cases of active tuberculosis. In 7 of these instances the patients were in the terminal stage of tuberculosis. These data support the assumption that the tuberculin test, properly performed, is an efficient instrument for the detection of active tuberculosis.

A similar study has been carried out by Musacchio<sup>200</sup> among 1000 persons with active tuberculosis. In this group 97.7 per cent were tuberculin-positive. Of the 23 who failed to have a cutaneous reaction, 17 had far advanced tuberculosis with cachexia, 1 had terminal bilateral renal tuberculosis, 1 had lumbar Pott's disease, 1 had pleurisy with effusion, 2 had moderately advanced tuberculosis, and 1 had only minimal tuberculosis with dry pleurisy. It is the author's opinion that the tuberculin reaction is positive in cases of active tuberculosis, both pulmonary and extrapulmonary, with few exceptions and that the overwhelming majority of positive reactors

are elicited by the first injection of 0.1 mg. of old tuberculin.

A study has been carried out by Dahlstrom<sup>201</sup> to determine whether the tuberculin reaction, once established, remains constant and, if not, to determine the factors responsible for its inconsistency. Of the group examined, 2490 were positive to tuberculin in at least 1 examination and 276, or 11.1 per cent, passed from the positive to the negative state during the period of observation in the dispensary of the Henry Phipps Institute. The lower the degree of sensitiveness, the greater was the likelihood of reversal from positive to negative reaction. Only 0.4 per cent of 1090 people who had a 3-plus reaction to the standard first dose of tuberculin became tuberculin-negative, whereas the negative state supervened in 70 per cent of 185 persons who had only a 1-plus reaction to the second dose. The greater the degree of family exposure, the more likely the reaction was to remain positive. In families with no history of tuberculosis in any member, 24 per cent of the members became negative, whereas among 63 reactors in families in which a patient with positive sputum resided constantly, only 1 person (1.6 per cent) became negative.

The tuberculin reaction never became negative in the group under consideration in the presence of lesions of active reinfection type tuberculosis, but it became negative in a small number of cases of tuberculous lesions of the type diagnosed by x-ray examination only. This latter group included 2 cases diagnosed as active childhood type tuberculosis, 5 cases with inactive or suspected reinfection type tuberculosis, and 11 cases with x-ray evidence of calcified primary tuberculosis. Of the total number of patients with recognizable tuberculous lesions of any sort, 0.72 per cent

showed a change in the tuberculin reaction from positive to negative. No significant correlation of instability of the tuberculin reaction with sex was detected, but there was definite correlation with age. The overwhelming majority of the unstable reactors were children.

It is generally stated that the cutaneous reaction to tuberculin has developed

opinions concerning tuberculin reaction will require revision if these observations are supported by other studies. The principal question is to what extent primary lesions can develop before a state of allergy to tuberculin has become manifest.

Since the discovery of tuberculin by Koch, it has been recognized that the injection of a sufficient amount of tuber-



Fig 14—Case 6, July 1, 1937. Essentially negative lung fields on admission. Child admitted because of chorea. Mantoux test given on date of this roentgenogram. (Lincoln and Grethmann J. Pediat.)

by the time that the primary tuberculous lesion is roentgenographically demonstrable. In contrast to this assumption, Levine<sup>202</sup> reports observations on 63 infants who contracted pulmonary tuberculosis under 1 year of age and who were followed from the earliest evidence of a primary complex to calcification or to death from tuberculosis. Sixteen of these 63 children had x-ray evidence of pulmonary infiltration prior to the development of cutaneous sensitivity to tuberculin. Since the cutaneous test is now accepted as the best diagnostic method for determining the presence of tuberculous lesions within the body, certain

tuberculin into a person with active tuberculosis could produce, in addition to the local reaction, a reactivation or increased activity of the tuberculous lesion, the so-called *focal reaction*. For this reason it has been common practice to employ only minute amounts of tuberculin for initial intracutaneous injections and to employ larger amounts only when the initial reactions were negative. The potential dangers of tuberculin tests in hypersensitive persons are again pointed out by Lincoln and Grethmann.<sup>203</sup> They emphasize that tuberculin is safer to use in well stabilized, even though extensive lesions, than in progressive or active

lesions, however small. They recommend an initial dose of tuberculin of not more than 0.01 mg. of old tuberculin. Furthermore, since it has been shown that patients who have progressive primary tuberculosis only rarely develop negative tuberculin reactions during childhood, a positive tuberculin test, once obtained, should not be repeated. They also suggest that when tuberculosis is

tutional disturbance. The gastric contents of 169 tuberculin-positive children were inoculated in guinea-pigs and tubercle bacilli were recovered in 76, or 45 per cent, of the cases. The clinical types of tuberculosis included in this series together with the per cent of gastric lavage findings of tubercle bacilli are shown in Table X. The important finding is, of course, the high number of in-

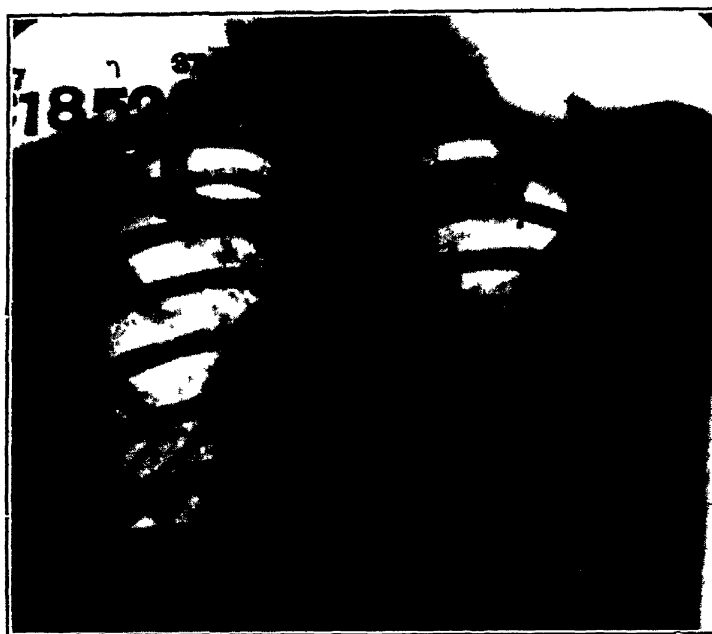


Fig 15—Case 6 Physical signs of pleural effusion at left base appeared 4 days after Mantoux test. Fluid obtained by thoracentesis was typical of tuberculous effusion. (Lincoln and Grethmann: J. Pediat)

suspected for any reason whatsoever, roentgenography, or at least fluoroscopy, might well precede a tuberculin test. Figs. 14 and 15 illustrate what is probably a focal reaction resulting from the injection of tuberculin.

**Bacteriologic Diagnosis** — Rosenkrantz and Hurwitz<sup>204</sup> have carried out a study to determine the diagnostic efficiency of inoculating guinea-pigs with the gastric contents of children with positive tuberculin reactions. As they point out, pulmonary tuberculosis in infants and children is a variable disease and may occur without any local or consti-

stances in which tubercle bacilli were found in the gastric contents of children who apparently had no demonstrable parenchymal lesion.

The technic employed by the authors was as follows:

After a 12-hour fast the stomach of the patient is washed out with 35 cc. of physiologic saline solution, on 3 successive mornings. This material (approximately 100 cc.) is collected in sterile bottles and kept in a refrigerator until delivery to the laboratory. It is then centrifuged in sterile tubes (50 cc. capacity) at 2650 revolutions per minute for 15 minutes and the supernatant fluid discarded. The sediment, usually 10 to 15 cc., is treated with 5 per cent oxalic acid, thoroughly mixed, and

TABLE X

GASTRIC LAVAGE FINDINGS IN RELATION TO THE VARIOUS CLINICAL TYPES OF TUBERCULOSIS  
(*Rosencrantz and Hurwitz. Am Rev Tuberc.*)

Type	Number of Cases	Number Positive	Per cent Positive	Remarks
Miliary	4	4	100	Two developed meningitis
Primary pulmonary infiltration . . . . .	38	35	92	Majority under 10 years
Pleural effusion. . . . .	12	7	58	Pleural fluid positive in 4 cases examined
Calcified parenchymal or lymph-node lesions	26	7	27	Small number of cases due to fact that majority are seen in clinic.
Hilar nodes . . . . .	66	16	24	These are patients where diagnosis of active pulmonary tuberculosis is difficult or impossible without lavage.
Extrapulmonary (4 bone and joint, 2 meningitis)	6	6	100	All showed intrathoracic involvement by x-ray—either hilum or parenchyma.

allowed to stand for at least 30 minutes at room temperature. It is then neutralized with 5 per cent sodium hydroxide solution plus a very small excess of the alkali to dissolve pus and mucus. Sterile saline is added and again it is centrifuged at 2650 revolutions per minute for 15 minutes. The supernatant fluid is discarded, and the sediment is washed twice with sterile saline (50 cc. each time) and centrifuged at the same rate and for the same time as previously. The final sediment is suspended in 1 to 2 cc. of sterile saline and inoculated subcutaneously into the groin of a guinea-pig weighing from 300 to 400 grams.

At the end of 6 weeks the guinea-pig is autopsied; in positive cases the regional and the retroperitoneal lymph-nodes and the spleen are enlarged. Smears for acid-fast bacilli are made from the pus of the infected nodes. Recently, the authors have been treating the 100 cc. lavage specimen with small amounts (0.1 Gm.) of papain. The mixture is allowed to stand at room temperature for 15 to 20 minutes with frequent shakings. This enzyme dissolves the mucus, thereby facilitating sedimentation of the solid particles (pus and bacteria) when the specimen is centrifuged. The remainder of the procedure is the same as outlined.

**Treatment**—On the basis of their own experience and that of others, Chadwick and Evarts<sup>205</sup> conclude that in the treatment of pulmonary tuberculosis in adolescents pneumothorax should be in-

stituted as soon as possible after diagnosis is made even in cases of minimal tuberculosis. Among the data cited are those of Morgan who reports a follow-up of 320 cases of tuberculosis in boys and girls between the ages of 10 and 18 years. Of the total group 62 per cent were dead, 14 per cent were still under treatment, 17 per cent were well, and 7 per cent could not be located. The treatment in this series was *prolonged bed rest* supplemented by *pneumothorax* in a few instances. When pneumothorax was employed, it was given only after a period of waiting to see whether the lesion would improve with rest. In contrast, reference is made to the report of Zacks who observed a series of 55 boys and 131 girls for a period of about 4 years. One group had routine sanatorium treatment only and another group had sanatorium treatment plus pneumothorax. The mortality in those who did not receive pneumothorax was 30.9 per cent for the boys and 34.4 per cent for the girls. Among those who received sanatorium treatment plus pneumothorax, the mortality was 8.5 per cent for the boys and 23.1 per cent for the

TABLE XI  
DETAILS OF SENSITIZING TREATMENT

Cases	Smallest Amt O. T. Giving Skin Re- action (mg.)	Time Under Treat- ment	No of Treat- ments	Amt O. T. Injected Subcutaneously (mg.)		Reac- tions	Acute Inflam- mation Disap- peared	Time Under Obser- vation	Vision at Dis- charge	Comment
				Smallest	Largest					
1. E. T.	0 0001	3 wk.	2	0 00001	0.0001	None	3 wk.	1 yr.	Good	Process gone
2. B. J.	0.0005	3 wk.	5	0 000001	0.1	None	3 wk.	2 mo.	R. 6/8 L. 6/12	Process gone
3 S. L.	0 0001	3 wk.	6	0 00001	0 0001	1	3 wk.	4 yr.	Good	No recurrence
4. O. T.	0 001	4 wk.	8	0 0001	0 01	None	4 wk.	8 mo	Good	No recurrence; acute in- flammation gone in 4 weeks
5. J. W.	0 000001	8 wk.	14	0 0000001	0 00007	1	6 wk.	12 mo.	Good	No recurrence; acute in- flammation gone in 6 weeks
6. W. J.	0 000001	7 mo.	32	0 00000001	0.01	6	3 wk.	19 mo	Good	No recurrence; acute in- flammation gone in 3 weeks
7. E. S.	0.000001	7 mo.	16	0 00000001	0.000001	3	5 wk.	24 mo.	Good	Acute inflammation gone in 5 weeks
8. G. B.	0 000001	4 wk.	6	0.00000001	0.000002	1	4 wk.	8 wk.	Good	Bilateral gray scars still present
9. D. B.	0 0000001	22 mo.	51	0 00000001	0.6	4	Still present	22 mo	Poor	Photophobia still present; process still active
10. C. S.	0 0000001	14 wk.	22	0.00000001	0 0007	1	3 wk.	22 mo	Good	
11. H. S.	0.0000001	11 wk.	17	0.00000001	0 0001	2	4 wk.	20 mo	Good	Acute inflammation gone in 4 weeks
12. A. G.	0 00001	6 mo	27	0.0000001	0.5	2	3 wk.	8 mo.	Good	
13. A. R.	0 0000001	4 mo.	6	0.000000001	0.0005	None	6 wk.	4 mo.	Good	
14. H. C.	0 001	8 mo.	8	0.0001	0.04	None	Still present	8 mo.	Poor	Process still active
15. J. W.	0 000001	8 wk.	5	0.000001	0.01	2	8 wk.	8 wk	Good in right	
16. F. P.	0 00001	3 mo.	11	0.00000001	0.00001	3	8 wk.	8 wk	Good in right	

girls. In the authors' group there was a mortality of 4.8 per cent for the boys and 27.5 per cent for the girls, or 21.7 per cent for the entire group. Of these, 50 per cent received pneumothorax.

It is on the basis of such data that the authors conclude that *pneumothorax* should be instituted even in cases of minimal tuberculosis among adolescents. If pneumothorax alone does not produce satisfactory collapse of the lung, *pneumonolysis* should be performed if there are adhesions that can be cut. A pneumothorax that is ineffective because of adhesions, or one that does not close a cavity, should not be continued. In such cases the pneumothorax should be abandoned and some other form of surgical collapse instituted. It is advised

that when a satisfactory collapse with pneumothorax is obtained, it should be continued for a period of at least 3 years, and for 5 years in the patients with pulmonary cavitation. Patients discharged from the sanatoria should be considered as having completed only the first phase of treatment and should return at frequent intervals for check-up. A roentgenogram taken every 3 months is the most important means of following the course of the disease.

### Conjunctivitis

**Treatment**—Although *tuberculin* is seldom employed at the present time in the treatment of pulmonary tuberculosis, it is still widely used for desensitizing treatment in *phlyctenular conjuncti-*



*vitis*. . A recent report, recording good results with this form of treatment, has been published by Howard<sup>206</sup> The children in this series had phlyctenular conjunctivitis as a manifestation of a tuberculous process. The author emphasizes the importance of the quantitative details of desensitizing treatment. In each instance the smallest amount of tuberculin to which the patient would react intradermally was determined and desensitizing injections were started at a

level below this point. When reactions were encountered either locally or at the site of injection or at the focus of infection, or generally, with rise of temperature, the amount of tuberculin injected was further decreased. In most instances, in the author's experience, the acute inflammation of the eye subsided in from 3 to 6 weeks and sight was restored except for an occasional corneal scar. The details of the author's treatment are tabulated in Table XI.

## WHOOPIING COUGH

By ROBERT A. LYON, M.D.

**Etiology**—The importance of a virus as a causative agent of whooping cough has been investigated further by Frawley.<sup>207</sup> He isolated a virus from the nose and throat secretions of a patient with whooping cough and injected it into the nasal passages of 12 children who had not had the disease previously. There was no reaction in 8, but the other 4 had a slight rise in temperature and symptoms of a respiratory infection, which in no way suggested whooping cough itself.

**Diagnosis**—The superiority of nasopharyngeal cultures over throat cultures or cough plate methods for the diagnosis of whooping cough has been demonstrated by Bradford and Slavin.<sup>208</sup> The nasopharyngeal cultures were taken by inserting a sterile swab on a thin copper wire into the nose until it touched the posterior nasopharynx. Of 25 children, 14 had positive nasopharyngeal cultures, 8 had positive cough plates, and 4 had positive throat cultures. In only 3 instances were the nasopharyngeal cultures negative when cultures by other methods were positive. The cultures made by the nasopharyngeal method often contained

more colonies of the pertussis bacilli than did the other cultures.

**Complications**—*Epilepsy* following pertussis encephalitis has been recorded by Worster-Drought.<sup>209</sup> A boy, 5 years of age, developed convulsions and other signs of encephalitis during the fifth week after the onset of whooping cough. Recovery from this episode was complete but 5 years later he had typical attacks of epilepsy. The author had observed epilepsy following encephalitis of measles and lethargic encephalitis, but this was the first instance in which pertussis seemed to be the etiologic agent.

**Treatment**—*Sulfapyridine* in the treatment of *pneumonia* complicating whooping cough gave favorable results in the majority of patients observed by Litter, Litvak and Givan.<sup>210</sup> Of the series of 22 patients with pertussis and *bronchopneumonia* who received the drug, only a few were not improved. The cause of the failure in 1 instance seemed to be the presence of a hemolytic anemia. In other cases, technical errors were responsible for the poor results. An omission of the drug occurred in 2 patients, and a failure or retention of the drug oc-

curred in 2 others. When a dose of the drug was delayed or omitted or was not retained by the patient, the first indication was apt to be a rapid elevation of the temperature. The difficulty of administration of sulfapyridine to whooping cough patients who vomited frequently raised a serious problem. In some instances, when the sulfapyridine was given in chocolate or malted milk or certain desserts, it was retained more readily. In other cases large doses which were given by rectum seemed to be absorbed adequately. *Complications* of sulfapyridine therapy in this series of patients included headache, dizziness, vomiting, cyanosis, moderate or mild depression of the leukocytes and in 1 or 2 instances a fever.

The value of *hyperimmune human serum* in the protection of animals against pertussis infections has been studied by Bradford and Wold.<sup>211</sup> Adults who had received recent injections of pertussis vaccine furnished blood serum which was concentrated and preserved by a lyophilic process. Injections of such hyperimmune serum into young mice simultaneously with saline suspensions of the pertussis bacillus protected a large number from death and produced much milder pulmonary lesions than observed in control animals. The administration of sulfapyridine alone or together with serum was ineffective in protecting the animals from the disease.

The administration of the *hyperimmune serum* to infants in the early stages of pertussis resulted in clinical improvement and in the augmentation of certain antibodies. Nineteen such infants and 3 older children were treated by Katsampes, McGuinness and Bradford.<sup>212</sup> Ten cubic centimeters of the serum were administered daily for 1 to 4 days. Phagocytosis and agglutinin titers were increased just as in convalescent patients, and there was a general

tendency for the number of lymphocytes to decrease.

Hyperimmune adult serum may be produced by the administration of vaccine to prospective donors. Such serum has been used in the prevention and treatment of pertussis by McGuinness, Bradford and Armstrong.<sup>213</sup> In their first series of 83 children who had been exposed to the disease, they administered 10 cc. of the serum to those who had been in less intimate contact and 20 cc. to patients who had been more intimately exposed. Only 18 or 22 per cent of the entire group developed the disease and the majority of the attacks were very mild in nature. This was much less than the expected rate of 70 per cent, which is the usual attack rate of exposed susceptible individuals. Another group of 100 patients in the early stages of pertussis received 10 to 20 cc. of the serum. In 32 patients the results were excellent, in 30 others the disease was only moderately severe, in 14 the results were doubtful, and 3 infants less than 2 months of age developed pneumonia and died. Best results were obtained when large amounts of serum were injected early in the course of the infection.

The presence of pertussis antibodies in *human convalescent serum* has been noted by Mishulow, Klein, Liss and Leifer.<sup>214</sup> Blood was taken from 38 patients recovering from whooping cough. Thirty of these samples protected from one-third to all of the mice inoculated with the bacteria. Little or no protection was obtained from some specimens of serum taken in the early weeks of the disease, but antibodies were usually present by the sixth week. Positive agglutination tests were obtained in the sera of 18 patients but the titers varied widely and there was no correlation between the protective power of the sera and the agglutination titer. The protec-

tive antibodies in the serum of convalescent patients tended to remain stationary for several weeks after the recovery of the patients and then diminished rapidly. In some instances the protective power had completely disappeared from the serum after a few months.

The presence of *agglutinins* in patients who have recovered from pertussis or have received the prophylactic injections has been confirmed by Miller, Jr., and R. J. H. Silverberg.<sup>215</sup> Employing a new technic, they observed that the sera of only 10 per cent of 101 children who gave no history of having had pertussis produced agglutination while that of almost all of a group of 164 children who had been vaccinated with pertussis vaccine, caused agglutination. The titers were maintained in many instances for a period of 38 months. The agglutination titers of 15 of a group of 17 pertussis patients were high at some time during the disease, but tended to decline rapidly in succeeding months.

The comparative value of various types of therapeutic agents in the treatment of pertussis has been reported by Cohen, Weichsel and Lapin.<sup>216</sup> More than 1000 patients were treated by one of various methods. Best results were obtained by the use of *convalescent serum* and with *hyperimmune serum*. Patients treated with this material had milder types of infection and recovered in shorter periods of time than those receiving injections of *Sauer's vaccine*. *Krueger's vaccine*, *nonspecific typhoid paratyphoid vaccine*, *nasal instillation of topagen* and subcutaneous injections of the same material did not seem to affect the course of the disease one way or another.

**Immunization** — Information concerning the effectiveness of immunization against pertussis by the *Sauer method* has been compiled by Doull,

Shibley, Haskin, Bancroft, McClelland and Koelscher.<sup>217</sup> The course of more than 400 children who had received complete courses of the vaccine was compared with that of a control group of comparable size, over a period of observation of 2½ years. The difference in the incidence of pertussis in these 2 groups was not great. About 18 per cent of the treated children and 22 per cent of the control series contracted the illness. A total number of 73 inoculated children and 62 control children had been exposed to the disease of siblings in their own homes. All but 1 of the control group contracted the illness, while only 56, or 77 per cent, of the vaccinated group had definite symptoms of pertussis, so that it seemed probable that the inoculations had protected 23 children from the infection. When the severity of the disease of the 2 groups was compared, the vaccinated children were found to have had milder attacks than the children of the control series. One death occurred in the control group and none in the treated children. The authors concluded that the inoculations had produced only slight effects in decreasing the incidence and severity of the infection.

Further observation of a large group of children who have been immunized with *pertussis vaccine* has been reported by Singer-Brooks.<sup>218</sup> Her group has been observed for a period of 4 years and every effort has been made to control the study accurately. She has taken into consideration the fluctuations of the incidence and character of pertussis in San Francisco throughout the years of observation and has given attention to the questions of intimacy of exposure of the children and the time and age at which the vaccine had been given. There was a tendency for the control group to be somewhat older than the treated

TABLE XII

SUMMARY OF RESULTS IN *HAEMOPHILUS PERTUSSIS* PHASE I VACCINE AND CONTROL GROUPS\*

Group	Total Number of Children	Number of Children Directly Exposed to Pertussis	Number of Exposed Children Who Contracted Pertussis	Communicability Rate (% of Exposed Children Attacked)	Difference in Communicability Rates	Standard Error	Number of Exposed Children Who Did Not Contract Pertussis	Protection Rate (% of Exposed Children Who Escaped)
H pertussis phase I vaccine (total dose 80 billion)	330	64 (19.4%)	5	7.8		. .	59	92.2
Noninoculated sibling or familial controls	200	45 (22.5%)	44	97.7	89.9 . .	±405	1	2.2

\* Summary of instances of exposures to, cases of, and escapes from pertussis which occurred in the group of children inoculated with *Haemophilus pertussis* phase I vaccine and their respective sibling or familial controls. The figures in parentheses represent the percentages of the total number of children in each group who encountered exposure to pertussis.

group. A total number of 330 children had been inoculated with the phase I vaccine and 200 children, mostly siblings of the above children, were not treated. Pertussis had occurred in 7.8 per cent of those who had been vaccinated and had been directly exposed to pertussis, and had occurred in 97.7 per cent of those who had been similarly exposed but not vaccinated. This difference in communicability rate was of significance from a statistical viewpoint. Observation over a longer period of time, however, was considered to be necessary in order to determine the effectiveness and the duration of the immunity conferred by the pertussis vaccine (Table XII).

Favorable results from whooping cough vaccination have been reported by Silverthorne.<sup>219</sup> Of a group of 97 vaccinated children who had been in direct contact with whooping cough, only 10 (10 per cent) contracted the disease. Of a group of 52 untreated children exposed to the disease, 43 children (82 per cent) contracted the illness.

Similar success from the active immunization of children by means of the *Sauer vaccine* has been obtained by Mitchell.<sup>220</sup> A group of 319 children who had received the inoculations were observed for a period of 1 to 5 years.

Whooping cough had developed in 1 to 15 per cent of the various groups during this period of time, with an average of 4.74 per cent in the entire group.

An evaluation of 2 types of whooping cough vaccine has been made by Lapin, Cohen and Weichsel.<sup>221</sup> In a series of 391 patients of their clinics and 266 children observed in private practice. *Sauer's vaccine* was given to 1 group of 180, a *toxic filtrate* from the research laboratories of the New York Department of Health was given to 165, and the remainder served as a control series. In respect to the complement fixation reaction, Sauer's vaccine produced a maximum response to antibodies in about 1 week after the last dose and a disappearance about 9 weeks later. With the toxic filtrate the complement fixation reaction persisted for a longer period of time. The attack rate of the disease in the inoculated children was about the same with the Sauer's vaccine as with the toxic filtrate but the disease was milder in patients of both groups than in those of an untreated control group.

The prevention of whooping cough in children who had been intimately exposed to the disease has been attempted with the use of various agents by Cohen and Lapin.<sup>222</sup> Ten children, exposed to

the pertussis of siblings, received daily injections of *Sauer's vaccine* in doses of 1 cc. a day for 1 week. Seven of these children contracted the disease and 3 did not. In a second group of 10 such children *Krueger's vaccine* was given in similar dosage, and again 7 contracted the disease and 3 escaped. This attack rate of 70 per cent is about that of untreated groups. Of a third group of 10 children who received *Mulford's topagen*, 6 contracted the disease. A fourth group of 13 children received 20 to 40 cc. of *blood serum* obtained from parents who had had the illness in previous years. In this group 8 children escaped the infection and 5 had mild forms of the illness. A series of 12 children had injections of serum obtained from individuals who had previously received considerable amounts of Sauer's or Mishulow's vaccine and 8 of these children were protected and 4 contracted mild types of the disease. Finally, there was a group of 33 children who received *convalescent serum* in doses of 5 to 40 cc. depending upon the age of the child. Only 5 of this series contracted very mild forms of the infection and with the larger doses of serum the results were very satisfactory. The authors concluded that the early administration of large amounts of hyperimmune adult serum or, preferably, convalescent serum, was highly effective in preventing pertussis in patients exposed to the disease.

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## PHYSICAL THERAPY

By JOHN S. COULTER, M.D.

### CRYMOTHERAPY

**Human Beings with Cancer Maintained at Reduced Temperatures of 75° to 90° F. (23.8° to 32.2° C.)—**Smith and Fay,<sup>1</sup> in their observations of these cases, state that urinalysis in all of the cases has shown nothing of pathological significance from the routine examination. No red cells or casts have been observed in any of the cases, and in the few instances in which more

careful analytical studies have been made chemically, no excess of any of the usual constituents has been observed during either the period of refrigeration or following it.

In this connection, autopsy studies upon cases ultimately dying of their disease have shown no evidence of damage to the glomeruli or tubules, as was feared might result from such exposure to cold.



Before the introduction of saline to maintain fluid balance, a reduction in chlorides had been observed. This has been corrected by the modified procedure.

Blood sugar, likewise, has shown a tendency to drop to the lower levels of normal, the average figure ranging somewhere between 80 and 90.

In the original report by Smith and Fay, the effect upon the respiration of these patients was noted. The rate tends to be somewhat irregular and shallow. Many of the patients show very little variation in actual rate, but others may show a drop to as low as 10 or 12, while still others may show an elevation to as high as 28 or 30.

In reviewing the physiological data which have been recorded both as clinical observations in respect to the patient's circulatory apparatus and respiratory system, and from laboratory studies, it became apparent that an entirely new field in human physiology has been opened for investigation. Previous to these studies, so far as the authors have been able to determine in a careful review of the literature, no comparable observations on human beings have been recorded. Indeed, it has been the general impression that any prolonged reduction of temperature below 94° or 95° F. (34.4° or 34.9° C.) was inevitably fatal. These studies have brought out the fact that patients can be maintained for periods as long as 5 to 8 days at temperature levels in the eighties, that relief of pain can be regularly anticipated for periods of time ranging from a few days to as long as 5 months, and that regressive changes in young embryonal cells, particularly in carcinoma, takes place as a result of lowered physiological activity, interfering with the metabolism of these cells.

These preliminary studies upon the physiological mechanism involved suggest that the entire body economy is reduced, that the circulatory rate and blood flow are slowed, and that the liver is in a relatively dormant and inactive state, as shown by the low nitrogenous analysis of the blood. Basal metabolism is apparently reduced by as much, perhaps as 20 to 25 per cent, and even lower figures may well be anticipated when special methods are devised for the more accurate recording of these observations. Just how far these alterations in physiology may prove of clinical value in medicine remains an entirely open question.

Thus far, these authors have observed what they feel to be beneficial effects in cases of *malignancy*, in cases of *drug addiction*, and in a single instance of *psychiatric derangement*. No doubt exists in their minds that the procedure is comparable in many respects to other major therapeutic methods and is not entirely devoid of risk. It is a method which certainly should only be attempted by individuals or groups where all available opportunity for careful observation of the patient can be carried out.

One thing stands out as a clear cut result of these studies, *i. e.*, the use of low temperatures in the control of *pain*. This is perhaps more particularly applicable from the clinical standpoint to chronic cases, especially to the terminal stages of cancer where patients are bed-ridden and such measures are more readily employed. Its usefulness in the therapeutic field otherwise remains a problem to be solved in the future.

Smith<sup>2</sup> gives a summary of the pathologic studies in a series of some 60 cases in which patients with cancer were subjected to local or general reductions of temperature and in which autopsies

were made. The studies are divided into 3 major groups, *i. e.*, (1) those relating to the normal body tissues; (2) those relating to tumor tissue subjected locally to temperatures of 40° to 50° F. (4.4° to 10° C.) for varying periods of time; and (3) those relating to metastatic tumor tissue in patients whose general temperature had been reduced to subcritical levels between 74° and 90° F. (23.3° and 32.2° C.).

Relating to the *first group* of non-neoplastic, or "normal" tissues, it may be said *a priori* that significant changes are the exception rather than the rule. In the series of 60 autopsies, marked myocardial degeneration was found in 5 cases. In 3 of these it was associated with definite sclerosis of coronary arteries. In 3 cases acute pancreatitis was seen; all 3 of the patients had been accustomed to take relatively large amounts of morphine. In 4 cases a significant and persistent fall in blood-pressure was observed; in 3 of these there was extensive bilateral adrenal metastasis. Bronchopneumonia, other than the terminal event commonly encountered in cases of advanced malignant disease, appeared chiefly in the postrefrigeration period, in association with metastatic involvement of the lungs. Its occurrence with and relationship to refrigeration, accordingly, is particularly difficult to evaluate.

With respect to the *second group*, temperatures of 40° to 50° F. (4.4° to 10° C.) applied locally to tumors regularly produced regressive changes going on to actual necrosis, even to the point of histologic clearance of the tissue of tumor cells in occasional instances.

In regard to the *third group*, the changes which were observed in metastatic tumor tissue from patients who were submitted to general reductions

of temperature to 74° to 90° F. (23.3° and 32.2° C.) were similar in kind but varied greatly in degree in comparison with those resulting from application of the lower temperatures locally. In no case were regressive changes encountered until 96 to 124 hours of refrigeration had been given, and in some cases no significant change seemed to occur after 300 hours of such low temperatures.

Vaughn,<sup>3</sup> in a study of experimental hibernation of metastatic growths, studied 6 patients with hopeless *metastatic carcinoma*, ranging in age from 26 to 52 years. The lowest temperature obtained was 83.2° F. (28.4° C.) rectal. The time spent in hibernation ranged from 9½ to 54½ hours. Basal metabolic rates were determined at the submerged temperature, the lowest being 84.2° F. (28.4° C.) rectal; the metabolism was lowered in every case in which the determination was made. The serious condition of the patient accounted for the shortness of the 9½-hour hibernation.

Primary carcinoma of the breast with metastases in the bones was the diagnosis in 4 of the 6 cases reported by Vaughn, while generalized carcinomatosis of the abdomen from primary carcinoma of the cervix and sigmoid colon accounted for 2 cases.

No deaths occurred during hibernation; 4 patients died between 24 hours and 3 weeks after hibernation.

Two patients are still living 7 and 8 months, respectively, after hibernation; they were entirely free from pain for 3 months and at present no narcotics are necessary to relieve their discomfort.

Vaughn concludes that the relief of *pain* was the only result of possible value found in the 2 patients still living; but it should be noted that these patients had had high voltage Roentgen therapy

preceding hibernation, which might in some degree be responsible for the relief of pain.

X-ray evidence reveals that 1 hibernation has not retarded the metastatic skeletal growth of carcinoma in these cases.

In his opinion, this procedure is hazardous and is not justifiable in the treatment of hopeless metastatic carcinoma.

## ELECTROTHERAPY

**Histamine Common Ion Transfer (Iontophoresis) in Varicose Ulcers—**Gould-Hurst<sup>4</sup> used a preparation of 2 per cent *histamine acid phosphate* in the treatment of varicose ulcers. His method of application is as follows:

A ring of skin  $\frac{1}{2}$  inch wide surrounding the ulcer is cleaned with spirit, and a thin layer of the histamine ointment is spread over one-half of this, the second half being reserved for the next treatment, because the skin so treated is apt to become somewhat sensitive. Care is taken at the first treatment not to allow the ointment to "spill over" on to the raw surface of the ulcer, because the rapid absorption of the histamine from a raw surface causes unpleasant symptoms, *e. g.*, flushing of the face, throbbing in the head, headache, palpitation, and even a feeling of faintness. So far he has only met 1 patient who could not, or perhaps would not, continue treatment because of unpleasant effects.

The semicircle of ointment having been applied, a pad of gauze soaked in warm solution is placed over it. The positive terminal of a galvanic battery is bound on to this pad, and the negative electrode is applied to some convenient adjacent area. A constant current of 4-6 ma. is slowly turned on, when most patients will say that they are conscious of a pricking sensation under the pad. This current is allowed to pass either for 5 minutes or until the patient complains of headache or other discomfort before the 5 minutes has passed.

At subsequent sittings both the amount of current passed and the time of the treatment are increased, but never pushed beyond a point of moderate headache. Head throbbing and flushing are generally pronounced, but the patient soon becomes used to this. These sensations should be explained to the patient before

the current is applied on the first occasion. A current of 10 ma for 12 minutes is about the average application that can be received with only the mildest discomfort, but many individuals vary considerably in their tolerance. After each treatment the patient rests for 15 minutes. Treatments are given twice weekly. A *dressing of sterile vaseline* or of *cod-liver oil* is then applied and the wound covered with gauze and firmly bound over a thin layer of wool.

After 2 or 3 such treatments the edge of the skin around the ulcer takes on a fresh pink appearance, and the ulcer begins to heal from without inwards. The skin of the leg in the immediate vicinity also becomes less brittle. Pain, which in some cases was continuous, rapidly diminishes until, after the fourth treatment, it has generally disappeared altogether. While the ulcer continues steadily to heal, the general outlook of the patient greatly improves, for undoubtedly the sight, and in some cases also the odor, of a raw ulcerated area, which refuses to heal, is very depressing and disabling. In 2 cases, the author found that healing proceeded normally until only a small ulcer about  $\frac{3}{4}$  inch in diameter remained. This refused to heal until the *histamine* was spread over the raw area itself.

The results have been uniformly successful, and the treatment seems to bring a sense of general well-being, unless it is pushed too hard. The average time taken for the ulcers to heal has been 8 to 12 weeks, and these were of very long standing which had refused to heal with other methods of treatment.

## Sinusoidal Currents

**Facial Paralysis and Its Operative Treatment—**Collier<sup>5</sup> states that the factors to be considered in every case of post-operative facial paralysis are the time of onset of the palsy, the electrical reactions of the facial muscles, and the condition

of the middle ear. Appearance of paralysis immediately after operation indicates complete interference with the continuity of the nerve and calls for operation as soon as the general condition of the patient permits. The shorter the time the facial muscles are denervated, the more perfect will be the results, the minimal tendency to mass movements and contractions.

If the facial movements have been observed after the operation and weakness is seen to develop 1 or more days later, it is safe and wise to wait; and, if a week or 10 days later the electrical reactions are normal, it may be assumed that the muscles have not been denervated, and that recovery will take place without interference. Here the damage must have been slight and the resultant edema insufficient to prevent conductivity. If, however, the reaction of degeneration is present 10 days after onset, it will be found that conductivity has been lost, owing either to severe compression or to section and loss of substance of the nerve; and, if the appropriate treatment is not given, recovery may never take place or, if it does, in the compressed cases it will be slow, incomplete.

*The indications for operating in the late cases, i. e., those seen several months or even years after injury, are less dogmatic. It is obvious that movement cannot be restored to fibrosed muscles; hence, loss of galvanic response is an absolute contraindication to any operation on the nerve. But the decision is more difficult when, although the nutrition of the muscles has been maintained by physical therapy, the lapse of time since the injury makes it likely that degeneration has taken place in the cells of the facial muscles. It is possible, but without post-mortem evidence no exact information is available that degenera-*

*tive changes in the nuclear cells proceed *pari passu* with fibrotic changes in the muscles. Every patient observed by the author in whom facial paralysis has persisted for more than 3 years has given a negative response to the galvanic test; hence, the question of nerve-grafting did not arise.*

Exploration is the only means of determining the site and the extent of the injury; if this is done from below at the stylomastoid foramen, the damage, if found in the descending portion of the nerve, can be repaired here by *decompression* or *graft* without damaging the tympanic membrane or the middle ear.

During the postoperative period the facial muscles must be supported by internal or by external *splinting* to prevent overstretching. The nutrition of the muscles is maintained by physical therapy, particularly heat. *Massage* must be directed to prevent elongation of the muscles. As soon as there is minimal return of active movement, careful *re-education* before a mirror, with relaxation of the sound side of the face, is the best safeguard against the development of associated movements. Here the cooperation of patient and masseuse is most important. Movements and not muscles are represented in the cortex, and voluntary control of movements can be learned. Collier believes that the training of individual movements is facilitated by avoiding the ordinary galvanic current, which can only stimulate isolated muscles and favors the development of tics and contractures.

***Paralysis of Serratus Magnus Muscle***—Overpeck and Ghormley<sup>6</sup> state that the function of the serratus magnus muscle is mainly to aid in fixing the scapula to the thorax when the arm is elevated, particularly anteriorly, and also to rotate the scapula in abduction and during for-

ward elevation of the arm at the shoulder. Stookey has proposed a more elaborate interpretation of the functioning of the serratus magnus muscle than is set forth in the foregoing sentence. He wrote that during elevation of the arm there are 3 cycles. The first is carried out by the deltoid and supraspinatus muscles; the second by the serratus magnus, trapezius, rhomboideus and levator scapulae muscles; and the third by the action of both the deltoid and supraspinatus muscles.

The most prominent symptom of isolated paralysis of the long thoracic nerve and the serratus magnus muscle is pain. Pain usually extends along the base of the neck and downward, over the scapular and deltoid regions on the affected side. The second most common symptom is the patient's fatigue on elevating the arm or the inability fully to elevate the arm.

On examination of the patient, the principal clinical observations are weakness of the pushing power of the affected shoulder and weakness of the abducting power of the arm above the horizontal plane. Winging of the scapula is always present when the arm is fully abducted or is elevated anteriorly.

Trauma was the chief causative agent in the author's series, 23 instances of the condition, or 82 per cent of the total number of cases, being the result of some type of trauma.

The authors use 2 types of *treatment*: conservative and operative. Various types of conservative measures may be tried, such as **supporting splints** and **bandages** and physical therapeutic measures such as **heat**, **massage** and **galvanic stimulation**.

Some type of **mechanical support** should be tried in order to relieve the patient of pain, if possible, and to relax tension on the serratus magnus muscle.

Persistent efforts in conservative measures may give the patient complete recovery, as is demonstrated by the follow-up observations on the authors' group of patients. **Reassurance** on this basis may do much to aid the patient's recovery. Certainly, **avoidance of heavy muscular effort** involving the affected muscle should be advised.

In this series, only conservative treatment was used, consisting of **physical therapy** and in addition, in some instances, **elevation of the arm** of the patient for a period of several weeks.

A follow-up of 15 patients indicated good results in 11 instances. There was complete recovery for 7 of these 11 patients, whereas 4 patients enjoyed recovery of strength but had persistent winging of the scapula. Three patients whose conditions were caused by trauma did not recover

## ELECTROSURGERY

**Endocervicitis** — Kleegman<sup>7</sup> states that in endocervicitis, there is a small group of cases where electrocoagulation and conization give results superior to the nasal tip cautery, particularly where there is a small external os, with a ballooned-out, chronically infected, endocervical mucosa beyond it.

1. **Electrocoagulation**—For this it is necessary to have a diathermy or radio tube machine and electrodes. Ende devised a good one, and Cherry has a modification of the Ende electrode. One disadvantage of the Cherry electrode is that because of the placement of the metal strips, raw surfaces are left in apposition and the possibility of subsequent stenosis is increased. After the canal is cleansed, dried and anesthetized, the electrode is inserted into the canal, pressed against the wall, and the current turned on for the required dosage. The handle is grad-

ually rotated until a coagulation of one-half the canal is obtained, 2 mm. in depth. Ende recommends that a gauze soaked in *enzymol* be left in the canal for 48 hours after this procedure. The other half of the canal is treated 8 weeks later. When necessary, treatment may be repeated at intervals of 8 weeks. For erosions and cysts, the bipolar electrode is used, and the superficial tissue between the tips coagulated.

For electrocoagulation of cervical erosions and endocervicitis in the late puerperium, Barrett prefers the radio tube machine with ball tip electrode causing electrocoagulation of the eroded area. Workers using this method have corroborated his excellent results. In a small series of extensive erosions of both lips, Kleegman has treated one of the lips with the nasal tip cautery and the other lip with Barrett's method and has found healing to be the same in both lips as to time and degree.

2. **Conization**—Hyams devised a technic whereby the infected glandular tissue in endocervicitis can be quickly excised, analogous to the Sturmdorf operation both as to tissue removed and degree of healing obtained. By both of his electrode with a fast cutting current, Hyams cones out the mucous lining of the cervical canal and its glands without injury to the underlying musculature. It is an office procedure and, when properly done, as simple for the patient as any of the others.

## EXERCISE

**Cardiac Disease and Edema**—Discussing the rôle of exercise in *cardiac disease*, Sussman<sup>8</sup> states that regular, moderate exercise delays the onset of cardiovascular disturbances in the normal. Judicious exercise as an adjuvant to the usual therapy in cardiac disease

helps to restore physical tone and psychic well-being, but unfortunately is a frequently neglected form of therapy. This statement is not to be interpreted as discounting the importance of rest, which obviously is still the basic therapy of anginal and congestive failure. Exercise must be individualized—never employed by the "rule of thumb." Frequently beneficial and occasionally even spectacular responses are noted in obstinate edema.

The author in discussing exercises for *edema* states that exercises may be started during the second week of treatment, beginning with simple deep breathing efforts with wide-open windows, followed in about a week with such leg exercises as have been employed in the treatment of peripheral arterial disease, and general massage except varicose legs. A few minutes of unsupported sitting in the bed, dropping the feet over the side of the bed and, finally after 8 weeks, even though the edema still be present, the patient is helped out of bed, seated upright in a chair with feet supported on an ottoman or stool. The same principle of postural changes is embodied in the *Sanders motorized bed* (see Fig. 1) with the added advantage in the latter of avoiding undue fatigue of the patient. Mental as well as physical improvement will be evident.

Standardization is not desirable. It is not a matter of great diagnostic acumen or clinical judgment on one hand, or a total hit and miss situation on the other. Vigilance and intelligence are more important than the character of the exercises. Labored breathing, cyanosis, prolonged tachycardia, a subjective sense of faintness or exhaustion are good clinical guides that exercises have been carried beyond the patient's tolerance, necessitating curtailing the program when repeated or preferably spreading out

over a longer period, possibly on a stagger plan

The author states that he does not intend to convey the impression that relief from the edema will be accomplished by exercise alone. Usual *drug therapy* is employed and high protein, fairly low fat and low starch *diet*, with *moderate restrictions of salt* is recommended.

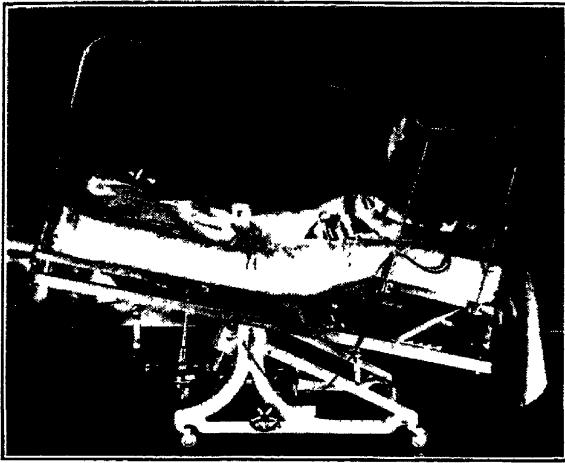


Fig 1—Tilting bed for Buerger's exercises (Sanders Vasocillator). Fitted also with an intermittent venous occlusion cuff device and a blanket cradle with a thermostatic heater to maintain accurate temperatures at patient's extremities.

One of the chief benefits of the exercise regimen is an increased desire for food, and treatment may be supplemented by the use of B or other *vitamins*. Whether or not a definite vitamin deficiency is accepted as a factor in the anorexia and epigastric distress, as pointed out by many authors, it is self-evident that some disturbance of nutrition is present.

Additional aid is obtained by the application of *crepe, elastic bandages to the legs*, prior to getting the patient out of bed. This probably helps the peripheral circulation. A daily trip in a wheel-chair to an *open-air sun porch*, permitting contact with other

patients, will result in genuine physical and psychic benefit.

**Exercise in Pulmonary Tuberculosis**—Habeeb<sup>9</sup> makes a plea for conservatism in the use of exercises for pulmonary tuberculosis. He states that in the treatment of tuberculosis the question of exercise occupies a place of primary importance. There is not a great deal written on the subject in the current literature. It might be thought to be a settled issue. There is, nevertheless, a wide divergence of opinion among tuberculosis physicians concerning exercise in the treatment of tuberculosis.

Those who believe in strict bed rest will consider every activity of the patient short of resting quietly in bed as exercise. Sitting up in bed, writing letters, drawing, knitting, etc., are exercise by that standard. By another standard, such activities are not considered exercise at all. Activity merits the designation of exercise only after the patient is fully clothed and is going for outdoor walks.

Any activity which produces severe fatigue should not be persisted in. Fatigue is a symptom of overstrain and indicates that the body needs more rest. To continue a given amount of exercise, no matter how little, day after day in spite of marked fatigue, is to court an increase in the tuberculosis.

Every case must be individualized. A blanket set of rules will not cover all cases. No 2 cases of tuberculosis are alike. It is obvious that patients with malaise, fever, rapid pulse, and marked fatigue should be on bed rest.

Patients with minimal disease and positive sputum, whether they have cough or not, should be in bed also. Exercise in such patients should not be permitted until a sufficient period of bed rest or a collapse measure in addition to bed rest has converted the sputum and

given the disease time to become stabilized.

In most sanatoria the amount of exercise is well regulated and the patient's activity is kept within safe limits. After the patient leaves the sanatorium, the advice concerning exercise is frequently disregarded.

The greatest necessity in the field of tuberculosis at the present time is a rehabilitation program.

**Exercises in Prevention of Pulmonary Embolism**—De Takats and Jesser<sup>10</sup> believe that one of the predisposing factors in thrombosis is a retardation of venous return from the lower extremities and pelvis. They state that efforts have been made from time to time to prescribe postoperative exercise, to turn the patient from side to side several times a day, to encourage deep breathing, to improve circulation time by thyroid extract and by digitalization of the failing heart. But a continuous gravity drainage of the endangered venous bed, aside from occasional notes in the Scandinavian literature, had not been advocated until the emphasis of Gray on the postoperative use of the *Trendelenburg position*. He raised the foot of the bed approximately 10 inches (25 cm.) for the first 24 hours after operation, with a view of improving pharyngeal and bronchial drainage and to encourage venous return from the extremities.

Since Gray's communication, the authors have placed all patients after a major operation in a Trendelenburg position for 24 and occasionally for 48 hours. Excluded from such a position must be patients with intra-abdominal suppuration or with cardiac failure, when such a position would lead to dyspnea. A 5 per cent angle can be accomplished readily by elevating the foot of the bed for from 8 to 10 inches. In case of shock, this

angle is usually increased to 10 degrees by doubling the elevation.

During the past 5 years 350 patients have been placed in this position at St. Luke's Hospital and the Illinois Research and Educational Hospitals. There was no postoperative thrombosis in this group, and the incidence of pulmonary complications as detected by clinical ex-



Fig 2—Postoperative exercise apparatus to improve venous backflow. The patient pedals on this stationary bicycle for 5 minutes 3 times a day, starting on the third postoperative day. (de Takats.)

amination was 3 per cent. At the same time a group of 1000 surgical cases at these institutions have showed 5 cases of postoperative thrombosis.

Besides diaphragmatic movements and abdominal distention, the inactivity of these patients is an important factor. To overcome this and to improve venous backflow by active muscular contractions, de Takats and Jesser have used ordinary *bicycle pedals* that are *mounted to the foot end of the bed* (see Fig. 2). The 2 shafts of the pedal have to be balanced. A washer prevents undue friction, and the pedals are placed in a wooden frame with a bracket rein-



forcement. The pedals can be tightened or loosened so that they can be used with more or less resistance. The patients pedal on this stationary bicycle for 5 minutes 3 times a day, starting on the third postoperative day. As these authors believe in relieving postoperative pains by enough *morphine* to insure deep breathing and avoid motionless rigidity in 1 position, only seldom has any objection been raised on the part of the patient. In fact, it serves in part as occupational therapy and encourages the patient to more active movement in bed. Regular breathing exercises and mild active movements of the lower extremities are equally effective.

This simple apparatus, which can be assembled easily at small cost, has also proved of value in mobilizing knee, ankle and hip joints, as an active vascular exercise and as a yardstick to measure intermittent claudication.

In the case of a suspected or manifest venous thrombosis, the exercise is naturally contraindicated. Nor can it be used if the necessary amount of motion causes pain. Following acute suppurative processes requiring complete immobilization, its use is obviously out of place. In the majority of instances, however, it is a simple and efficient method to promote venous backflow and to counteract inactivity.

**Thromboangiitis Obliterans — Buerger's postural exercises,** according to La Fevre,<sup>11</sup> should be used routinely in the treatment of patients with thromboangiitis obliterans. The patient is trained to do these exercises in the hospital twice daily for an hour at a time, and is instructed to continue them at home. They consist of alternately elevating the feet at an angle of 60° for 3 minutes, then allowing them to hang over the bed for 3 minutes, and finally

resting for 3 minutes, when the process is repeated.

The positive and negative pressure apparatus has been widely used for the treatment of peripheral vascular diseases. Its use in thromboangiitis obliterans, however, especially in cases with definite vasospasm, has not been satisfactory. In selected cases, it may be helpful as an adjuvant. More recently, the apparatus producing intermittent venous occlusion has been recommended. La Fevre's results with this appliance have not been more satisfactory than with the positive and negative pressure apparatus. The use of a blood-pressure cuff pumped up above diastolic level for regular periods of 2 to 3 minutes, and then released, has occasionally been helpful and is a simple method of producing intermittent venous occlusion.

Ochsner,<sup>12</sup> in discussing peripheral vascular diseases, states that vascular exercises are of value in some cases. Buerger originally described the exercises known by his name and found that when systematically used, they were of distinct benefit in the promotion of collateral development. Probably of more value than the Buerger exercises are those exercises obtained by means of a *tilting bed* (see Fig. 1). This is particularly true in patients who have progressive lesions and who are confined to bed. Passive vascular exercises by mechanical devices have been used extensively in the treatment of peripheral vascular disease. This form of therapy probably is of greatest relative value in those patients with degenerative organic disease because they have little or no associated spasm. Veal has shown, however, that while this method of therapy may be beneficial in patients with extensive collateral circulation, it is of little or no value in those cases where there is marked diminution of the vascular bed. The method obvi-

ously has distinct limitations, because these patients are in greater need of circulatory improvement. Kountz found that little benefit is derived from the use of this machine and de Takats and Veal believe that the degree of involvement present at the onset of treatment is the most important factor in the determination of the degree of benefit which may be obtained by this form of therapy.

Based upon the original observations of Bier, Moszkowicz and Matas, and the extensive studies of Lewis and his co-workers on the principles of reactive hyperemia, *intermittent venous occlusion* has been developed as a simpler and less expensive method of therapy than passive vascular exercises. Here, again, the limitations of this form of therapy are much the same as for the passive vascular exercises. De Takats found that it had no beneficial influence on pure vasospastic functional disturbances and its limited value has also been indicated by others.

### Foot Exercise

Ober<sup>13</sup> states that to prescribe exercises for a *painful, uncomfortable foot* which is already overburdened does not seem sound therapy. When the symptoms have been relieved, however, exercises are indicated. They are also indicated in the *weak, pronated feet* of children and adults. Too many patients become easily discouraged with foot exercises and give them up long before benefit can be expected. The reasons for this are boredom, lack of interest in prolonged treatment, and too many exercises to be done at a time. If the exercises can be boiled down to a single maneuver, the surgeon will get more cooperation. This maneuver will increase the tone of all the muscles that control the arch of the foot. The patient is

shown how to flex all his toes strongly and at the same time he dorsiflexes, adducts and inverts the foot. This position is held momentarily. The contracted muscles are relaxed slowly and the contractures are repeated several times, morning and evening. It will be found, in the long run, that more patients will perform this combined exercise than they would do a dozen different exercises 10 times each.

Ober further states that it must be perfectly obvious, even to the uninitiated, that no special type of shoe can be designed to solve all the difficulties of a painful foot. The patient should be told to go shopping for a shoe that is comfortable on his feet; in most instances, some alteration can be made in that shoe to make it fit more perfectly. This can be brought about in several ways. The heel can be raised all over, in order to compensate for the patient's loss of passive dorsal flexion. If there are bunions present, the area over the bunion can be stretched as much as  $\frac{1}{2}$  inch, if necessary. The shank of the shoe can be brought up to the patient's arch by removing the old shank and inserting a longer, higher shank of untempered steel, which can be raised or lowered, as necessary, until the sole of the shoe is touching the arch of the foot. After a few days' trial, if the shoe is comfortable, the shank is removed and a plaster mould is made of it. The shank is now tempered, refitted to its cast, and then placed permanently in the shoe. The cast is kept for future shanks.

When the symptoms of *foot strain* are more severe, it will be necessary to use an arch support made of leather, felt, sponge rubber or metal. There are some fundamental principles involved in fitting supports to painful feet. Elderly persons cannot stand hard supports, and

children do better with supports that are flexible. The chief object in fitting a support to a patient's foot is to supply a device which will make a comfortable shoe fit that individual foot more perfectly. The arch support which can be purchased in a store will not answer the purpose for long, because experience has shown that such supports usually furnish only temporary relief from pain. When the pain returns, it needs an expert to make further adjustments in any support so that it will continue to give relief as the foot improves. This improvement does not mean that the arch of the foot gets increasingly higher. It does mean that the abnormal position of the foot improves and, as a result, the support no longer fits but must be adjusted; otherwise the patient will be uncomfortable.

Sometimes there is so much pain from foot strain that no form of shoeing or altering of the shoe will give relief. In such instances it is best to keep the patient off his feet entirely until the pain has gone. Ober believes that in the most severe cases metal supports are necessary.

One of the stated objections to the *metal plate* is that it causes atrophy of the foot. There is no reason to uphold this theory if the foot is properly supported by the shoe and the plate. If the plate is truly a source of atrophy, then any supporting device will cause atrophy. Is it not also true that atrophy occurs in the untreated painful foot? In the milder cases of foot strain the shoe recommended for the normal foot will serve, especially if the shank is raised from time to time as improvement of the foot progresses. Raising the inner border of the heel will help to correct the pronated foot and may be incorporated in the methods described.

## FEVER THERAPY

**Multiple Sclerosis — Results of Treatment**—Bennett and Lewis<sup>14</sup> have followed 51 cases of multiple sclerosis for an average of 31 months after artificial fever therapy.

These 51 patients have been classified as early, intermediate and advanced, the first group being of short duration and ambulatory without assistance, the last bedridden and usually of long duration.

Of the 10 classified as early cases, 8 experienced and maintained worthwhile improvement. In 4 of these the findings were such as to suggest an infectious basis, so that they were not easily distinguished from acute encephalomyelitis. These 4 all went into almost complete remission which has been maintained. Of the other 6 *early cases*, 4 received definite prolonged improvement. The results in 10 early cases seem better than what might have been expected with no treatment at all.

The 25 *intermediate cases* showed slight to marked improvement in 13, of whom all are still engaged in full or part time occupation. Although these results appear rather good, it is pointed out that in a group of 53 patients with multiple sclerosis of all types, followed for 4 years with no treatment whatever, at least 22 were still ambulatory, many of them working. The results in this intermediate group are, therefore, not very different from the probable results without treatment.

In the 16 *advanced cases* only 2 showed any definite halting of the progress of their disease, and a few seemed to be made, at least temporarily, worse by the treatments.

The rôle of accessory quinine treatment in these 51 cases was evaluated. Since in both the improved group and the unimproved group about one-half of

the patients received quinine, it is difficult to attribute to this drug any significant influence on the clinical results.

The progress of individual symptoms was followed in 41 of the 51 cases. These 41 showed 168 symptoms; of 97 symptoms of 2 years' duration or less, 61 per cent improved; of 71 symptoms of longer duration, only 25 per cent improved. Twenty per cent of the symptoms have become worse, but curiously, only 5 patients reported new symptoms. Although this may be an understatement, it was generally noted that in patients whose disease progressed clinically, the progression was usually by advancement of old symptoms rather than by the appearance of new ones. In none of the 8 early cases evaluated was there progression of old symptoms or appearance of new ones. Of the 12 patients in whom the 32 increased symptoms were distributed, 9 were advanced and only 4 intermediate.

On the whole, except in the early group of cases and those having signs which suggest infection, there is little evidence that fever therapy has any markedly beneficial results in multiple sclerosis. This is probably true, no matter what the mode of fever production. Particularly do the results obtained not bear out the reports of Neymann and his collaborators of marked and sustained improvement from fever therapy.

The authors conclude that these results in 51 cases of multiple sclerosis treated by fever therapy indicate that it should be tried in early cases, of short duration and ambulatory without assistance.

In the intermediate types requiring assistance to be ambulatory but not completely disabled, the benefits derived from fever therapy are doubtful. Other less vigorous methods of therapy are indicated.

In the bedridden group, in which the completely disabling symptoms are of long duration, fever therapy does no good and may do harm.

**Paresis—Results of Treatment—**Fever in the treatment of syphilis of the nervous system has been studied by O'Leary and his associates<sup>15</sup> from a total of 1420 patient records; of these, 1100 patients were treated with malaria and 320 with artificial fever.

Prior to the administration of fever therapy, the diagnosis of paresis or of taboparesis was established for each patient. In evaluating the results of therapy among patients with taboparesis, only the responses of the paretic symptoms to the therapy have been considered.

The term "*paresis*" in this study refers to the symptom-complex caused by syphilitic meningoencephalitis, characterized by distinctive psychiatric, neurologic, serologic, and spinal fluid abnormalities. Among the patients with mild and intermediate paresis, there were no statistically significant differences between the rates of remission obtained under malaria and those obtained under artificial fever therapy. Sharp and statistically reliable differences were noted between the results of the 2 methods of therapy among patients with severe paresis on beginning treatment.

The earlier in the course of the disease the fever therapy was instituted, the more favorable were the clinical results. By the conclusion of 3 or 4 years of treatment-observation, more than one-half the patients with mild paresis treated with either method of therapy were clinically "cured." The chances of clinical recovery with either method of therapy were reduced to approximately 1 in 4 for patients with intermediate paresis. The remission rates for patients with severe paresis treated and observed

for the same length of time, decreased approximately 1 in 100 under malaria and 10 in 100 under artificial fever. Proportionately more clinical progressions occurred in patients with severe paresis under malaria than under artificial fever therapy. Except for the better clinical response to artificial fever in patients with severe paresis (more clinical remissions and fewer clinical progressions), there were no other statistically reliable differences in the clinical results obtained with the 2 types of therapy.

For purposes of this study, the authors defined as treatment deaths not only patients who died during fever therapy, but also those who died regardless of cause within 3 months of treatment. Under this definition the total crude death rate was higher with malaria (13 per cent) than with artificial fever (8 per cent).

Regardless of the method of therapy, the percentages of reversal, both in spinal fluid and in blood, increased as the duration of treatment-observation grew longer. Spinal fluid reversal rates at the conclusion of each of 4 annual periods were not only more rapid, but approximately twice as frequent under malaria as under artificial fever. Positive blood reversed more rapidly though not in greater proportion than positive spinal fluid. The percentage of blood reversals was greater in the malaria-treated group but not so rapid as in the artificial fever group.

The more abnormal the spinal fluid, the less responsive it was to any type of treatment. It was found, however, that proportionately as many patients treated with malaria as with artificial fever had strongly abnormal (paretic type) spinal fluid.

To determine the effect of *chemotherapy*, the patients under study were

divided into 2 major groups: those receiving no chemotherapy and those who were given chemotherapy in addition to or in connection with fever therapy.

The percentages of spinal fluid and blood reversals in the malaria and artificial fever therapy patients not receiving chemotherapy were similar. None of the differences were statistically significant. Among those patients treated with chemotherapy, better results were observed in the malaria than in the artificial fever group. These were statistically significant.

All patients treated with artificial fever were classified into 4 major groups based on the average duration and intensity of fever:

*Group A*—Minimum duration and intensity of fever: An average total of 30½ hours above 101° F. (38.3° C.); an average of 12.8 sessions of 2½ hours comprising the total course; maximum temperature at 104.9° F. (40.5° C.); an average of 26 percent of the total fever time at a level between 104° and 104.9° F. (40° to 40.5° C.).

*Group B*—Maximum duration and moderate intensity of fever: An average total of 69 hours above 101° F. (38.3° C.); an average of 10.3 sessions of 6½ hours comprising the total course; maximum temperature at 105.9° F. (41° C.); an average of 38 percent of the total fever time at a level between 105° and 105.9° F. (40.6° to 41° C.).

*Group C*—Moderate duration and high intensity of fever: An average total of 56 hours above 101° F. (38.3° C.); an average of 7.8 sessions of 7 hours comprising the total course; maximum temperature at 106.9° F. (41.6° C.); an average of 41 per cent of the total fever time at a level between 106° and 106.9° F. (41.1° to 41.6° C.).

*Group D*—Moderate duration and maximum intensity of fever: An average of 44 hours above 101° F. (38.3° C.); an average of 5.5 sessions of 8 hours comprising the total course; maximum temperature at 107° F. (41.7° C.) or above; an average of 57 per cent of the total fever time at a level between 106° and 106.9° F. (41.1° to 41.6° C.) supplemented by an average of 8 per cent at a level of 107° F. (41.7° C.) or above.

The data indicate that the best results were obtained by the patients treated under the average fever time and intensity described under group C. Although equally good clinical results were obtained by patients classified under group D, the higher intensity of fever administered to patients in this group did not increase the percentage of clinical remissions. The patients in group C were further subdivided into 2 groups, *i. e.*, groups C-1 and C-2. The maximum intensity of the artificial fever administered to patients in group C-1 ranged from 106° to 106.4° F. (41.4° to 41.3° C.), while among patients included under group C-2 the maximum temperature ranged between 106.5° and 106.9° F. (41.4° and 41.6° C.). The percentages of clinical remission obtained by patients in groups C-1 and C-2 were similar. It may be concluded, therefore, that no clinical advantages were gained by submitting patients to temperatures of 106.5° F. (41.4° C) or above. This observation is particularly important, since the writer is of the opinion that temperatures between 106.5° and 106.7° F. (41.4° and 41.5° C.) are apparently the highest safe temperatures that can be used in clinical practice, and then only when surrounded by safeguards.

## HEAT

**Arteriosclerosis Obliterans** — The correct use of heat and massage in this condition is summarized by Wright,<sup>16</sup> who states that the trend in recent years has been toward conservative therapy as against radical surgery. Marked success has resulted from this trend in the treatment of the organic occlusive disease thromboangiitis obliterans. The major amputation rate, which formerly averaged about 70 per cent, now ranges between 3 to 10 per cent in several lead-

ing vascular clinics. Arteriosclerosis obliterans has been less responsive to conservative therapy for numerous reasons.

Wright believes that in spite of these handicaps, definite improvement in the amputation rate has been achieved by the selective and considered use of the following important technics and medications:

1. **Rest** of the involved extremities *in a controlled temperature* of from 88° to 94° F. (31.1° to 34.4° C.).
2. **Soaks and baths** at similar temperatures, using only mild solutions, such as *saline, boric acid or azochloramide in triacetin* 1:500.
3. **Heat applied to the abdomen**, producing reflex vasodilatation.
4. **Postural exercises**, preferably passive, by means of the oscillating bed described by Sanders (see Fig. 1, p. 573).
5. **Pressure-suction boots** in a few selected cases
6. Alcohol in the form of *spirituous liquors* by mouth.
7. **Deproteinized** and other *pancreatic tissue extracts* by intramuscular injections.
8. **Extreme general care in the protection of the feet.**
9. **Meticulous attention to any open lesions**, using only correct technic in their care
10. **Control of diabetes or other complications.**
11. The judicious use of the *sulfanilamide* compounds in the presence of infections, selection being based on the organism present, if possible.

## Myositis Ossificans Traumatica—

In discussing the use of heat in this condition, Thorndike<sup>17</sup> believes that it is not only the type and severity of the original contusion, but also the diathesis of the patient that produced "myositis ossificans traumatica." The *preventive measures* are those primarily designed to *protect the individual from* the possibility of obtaining such *injuries in sports, i. e.*, proper padding and such protection as is permitted by sport rules and regulations. The second important point in prevention is the immediate in-

stitution at the time of the injury of proper measures to *control hemorrhage*, i. e., the *application of cold* for 1 hour and the use of a *compression bandage with sponge rubber*. The third point is the ruling out of massage in the early treatment of all deep-muscle contusions. Greater areas of ossification have been produced by overenergetic massage in the early treatment of ordinary muscle contusions. It is a far safer rule never to apply massage directly to the area of tenderness in a muscle contusion.

The author concludes that myositis ossificans traumatica is an inflammatory process of muscle in its early stages and before ossification is actually demonstrated by the Roentgen ray. "Tumor," "dolor," and "calor" are all present at this stage. This inflammatory process gradually subsides as ossification takes place. The ossification is gradually absorbed in part and sometimes in full, depending upon its size and location. The muscle function returns to normal, except in those instances where the ossification occurs near a joint.

Treatment necessitates the immediate *application of cold* and a *compression bandage* to control hemorrhage, and later *heat* to aid in the absorption of the hematoma. Of great importance is the *avoidance of massage on all severe and tender muscle contusions*. *Operative removal of the ossification* is indicated only in those cases in which it occurs near a joint in the origin or the insertion of a muscle, where joint function is permanently impaired, and then only from 12 to 24 months after the injury.

## HELIO THERAPY

**Tuberculosis of the Spine**—The value of heliotherapy in spinal tuberculosis is stressed in recent literature. Amberson<sup>18</sup> in a consideration of the

pathogenesis and medical treatment of tuberculosis of the vertebrae states that there is no substitute for the general scheme of *rest treatment* in any form of tuberculosis, and it is particularly important in the case of recently developed disease. Proof of the value of rest treatment is empirical. It should not be supposed that this consists solely of rest of the local lesion. Healing depends not only on this, but also in the preservation and enhancement of the general specific and nonspecific factors which enter into resistance. Their vital importance is best demonstrated when they are impaired, as by malnutrition, fatigue, worry, menstruation, pregnancy, associated diabetes, and many other causes. Rest treatment, therefore, should include, if possible, the elimination or minimization of such deleterious influences in order to ensure the maintenance of vital resistance at a maximum level.

Physical agencies, such as *heliotherapy*, *balneotherapy*, and *climatic treatment*, are useful for their effect in preserving and stimulating physiological tone and in promoting mental and physical relaxation. Except for certain superficial tuberculous lesions, it is doubtful whether natural or artificial heliotherapy is lethal for bacilli in the tissues or that it accelerates healing in a specific way. *Psychotherapy* is important to help the patient resolve his personal problems, which otherwise may act to retard his progress. Serenity and calmness are powerful factors in promoting recovery.

There is no substitute for time in the healing of this disease, and even several years is not too long a period when the alternative of repeated relapses, chronic invalidism, and early death is considered.

Meyerding<sup>19</sup> believes that operation to produce *surgical fusion of the*

**spine** is a comparatively safe procedure. It may be performed without danger of aggravating the disease process. It aids in giving stability to the diseased portion of the spine. It does not necessarily prevent extension of the disease, formation of abscess, irritation of the spinal cord, or paraplegia among patients whose resistance is not good. It is best to delay spine fusion for children who are sick; when the process becomes quiescent, spine fusion can be employed as an internal splint to aid in ankylosis. The results of spine fusion as a treatment for tuberculosis of the spine are probably better in adults than in children. An operation that produces fusion of the entire region of involvement gives better immobilization and, consequently, better results than does one that effects fusion of a more limited region. It is often impossible, in the early stages of tuberculosis of the spine, to determine the exact extent of the process either by clinical or by roentgenographic examination.

At the end of 5 years, 396 of 480 patients observed by Meyerding had been traced; of these 396 patients, 63.64 per cent had returned to an occupation; 7.83 per cent had obtained improvement, 2.79 per cent had had temporary improvement with relapse later, 6.31 per cent had had no improvement, and 18.43 per cent had died.

The best results are obtained when patients are carefully selected for operation, when spine fusion is employed during the period of healing of the disease, and when such treatment is reinforced by conservative treatment for a prolonged period of time.

The paramount requirement for every patient who has tuberculosis of the spine is *rest, heliotherapy, and a nutritious diet*. No surgical treatment can offset the value of conservative treatment.

In a critical study of tuberculosis of the spine in children, Mayer<sup>20</sup> states that as a result of 15 years of observation of these cases it is impossible to make a certain diagnosis of tuberculosis of the spine in the early stage, since other diseases may give similar symptoms, physical signs, and roentgenographic appearance.

Since the virulence of the invading tubercle bacillus and the resistance of the patient are 2 variables, the medical observer must be extremely cautious in attributing an early arrest of the disease to any one factor in the treatment. This applies particularly to the effect of fusion.

Since spine fusion involves only the laminae and the intervertebral articulations, and because the healing of the invaded bodies usually takes place by the so-called block process in which a fusion of one or more bodies occurs, the operative fusion, if performed at a stage antedating the pathological fusion of the bodies, will, if the fused laminae prevent flexion, actually tend to interfere with the natural process of healing.

Despite the great advance of medical knowledge, the essentials in the general treatment of tuberculosis of the spine remain today the same as in the time of Hippocrates—*fresh air and sunlight, nutritious food, and adequate rest*.

A case of tuberculosis of the spine cannot be declared cured because of the disappearance of muscle spasm, tenderness, and pain. It is reasonable to assume a cure under the following conditions:

- (a) Disappearance of abscesses or their calcification, as seen in the roentgenogram
- (b) Block formation of 2 or more bodies
- (c) Closure of sinuses
- (d) Absence of pain, temperature, and muscle spasm
- (e) Consistent gain in weight.



**Genital Tuberculosis** — Thomas, Stebbins and Rigos,<sup>21</sup> in a discussion of genital tuberculosis, declare that the statements made and the opinions expressed are based on the following: (1) The data obtained during repeated urological examinations and the clinical data in the records of many patients who had some lesion of genital tuberculosis and who were observed at Glen Lake Sanatorium; (2) the pathological study of tissues removed during surgical treatment and at autopsy; and (3) a study of the data obtained from the autopsy protocols of 17,777 consecutive autopsies done by members of the staff of the Department of Pathology of the University of Minnesota.

Before treatment for lesions of tuberculosis in the genital tract is undertaken, the patient should be thoroughly examined for evidence of other lesions of active or quiescent tuberculosis. The urogenital tract should be thoroughly examined for evidence of lesions elsewhere in the genital tract and for the primary lesions in the kidneys. When the data obtained during these examinations are at hand, the treatment of the genital lesions may be planned. When active lesions are found in the chest cavity or elsewhere, hygienic treatment only should be started. Most patients with any lesion of tuberculosis will gain if they are put at *rest* in bed. **Heliotherapy** may be used if this is indicated and if it is beneficial to the patient.

If a *renal lesion* is found, this should receive appropriate treatment before treatment of the genital lesion is started. The surgical or other treatment of a renal lesion plus continued hygienic treatment after surgical operation will control and arrest lesions in the prostate gland.

Tuberculosis of the *seminal vesicle* will recover without surgical treatment

if tuberculosis of the kidney is brought under control and hygienic treatment is practiced long enough.

Thomas and his associates reach the following conclusions:

1. Tuberculosis of the genital tract is a local manifestation of a general disease and lesions here are most often secondary to a primary urinary tract infection in the kidney. The treatment plan of the local genital lesion or lesions must be based on this pathological fact.

2. The route of spread from the kidney to the genital tract is most often *via* the urine.

3. The primary lesion in the genital tract is most often the prostate gland. From here the infection may spread to the other genital organs. Foci of tuberculosis in the prostate gland may produce no symptoms.

4. The seminal vesicle is infrequently infected with the bacilli of tuberculosis and is most always associated with lesions of tuberculosis in the prostate gland.

5. Tuberculosis infection in the epididymis is secondary in the genital tract to tuberculosis in the prostate gland. There may be a subacute stage of tuberculosis of the epididymis which is activated by trauma.

6. Treatment of lesions of tuberculosis in the genital tract consists of:

- (a) The location and arrest of other lesions of tuberculosis and of the primary focus in the urinary tract by whatever means are necessary.

- (b) **Hygienic treatment** of lesions of tuberculosis in the *epididymis* and **heliotherapy** to be followed by application of **heat, incision** and **drainage**, and **surgical removal** when indicated.

- (c) Orchidectomy is rarely necessary.

- (d) **Hygienic treatment** for tuberculosis of the *prostate gland* and *seminal vesicles* after removal or arrest of other active foci in the urogenital tract is always practiced. Surgical removal of these organs is seldom necessary.

- (e) **Postoperative rest** for 3 months is always essential.

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## MASSAGE

**Muscle Lesions Simulating Visceral Disease**—Harman and Young<sup>22</sup> describe a condition in which massage is an essential part of the treatment. They

state that it is common knowledge that disease of structures of the back, such as Pott's disease, carcinomatous deposits in the spine, and osteoarthritis may cause pain in the abdomen, because the disease will sooner or later become obvious. Muscle lesions, however, will be missed completely if not thought of, because they never declare their presence by disablement or death, and there is not even an abnormal radiogram to suggest a diagnosis. They will be wrongly diagnosed or looked back on merely as obscure pains which came and went and caused no harm. Nevertheless, they have been recognized before as mimics of angina pectoris and headache, and doubtless many practitioners have their own experience of similar traps in diagnosis. From the author's cases, they point to the imitation of *carcinoma of the colon*, *hydronephrosis*, *chronic appendicitis*, etc. The lesions affect various muscles, and the pain may be diffused to almost any part of the body, yet they have their own peculiarities and natural history, and it is better to regard the syndrome as more characteristic of itself than of a host of other diseases with which it may be confused.

Twenty-four cases, summarized by the authors, have been collected in which an affection of the back caused pain in the front of the abdomen and chest and led to an erroneous diagnosis of visceral disease. The mechanism of this false localization is discussed in relation to recent work on deep pain sensation. The lesions are shown to have been in muscles, and it is suggested that they were similar to "rheumatic" affections.

Treatment is effective enough to make it an essential part of the diagnosis; it consists of infiltrating the lesions with *procaine*, supplemented by *massage* and *exercises*. The pain and its usual variations and associated phenomena are

described, and it is held that the syndrome is sufficiently characteristic to suggest a correct diagnosis. This can be confirmed by discovering the muscle lesion responsible

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## OCCUPATIONAL THERAPY

The operations of the highly diversified program of physical education carried on over a period of 17 years at the Veterans' Administration Facility, Perry Point, Maryland, are reported by Campbell and Davis.<sup>23</sup> The rationale of *play* as a general balancing and reparative agency has been studied and well presented and the writers do not discuss its purely psychological setting, but rather indicate what appear to be certain distinctive applications of physical educational methods to the increasing armamentarium of therapy

A wide category of both formal and informal activities has been attempted for the acute mental service, including calisthenics, swimming, gymnastics, soft ball, volley ball, impromptu games, such as medicine ball circle passing. Of the 40 patients on the ward, ranging in chronological age from 35 to 40, 38 participate in some form of physical therapy, 20 take part in forms of social play, while 18 confine their activities to the more mechanical and individual types of exercise, such as swimming and calisthenics; 18 play in the soft ball league. A very definite line of social demarcation is observed between the groups who are able to find elements of extraversion in their play experiences and those who retain their antisocial predominating traits. Eleven patients appear to show some improvement in their social readjustment, as evidenced by some of the following: (a) Greater modifiability to social practices; (b) increased range of

interest; (c) greater control of emotional field; (d) more co-operativeness; (e) more insight; (f) brighter attitude; (g) increased range of physical activity; (h) stronger volition. The primary motif for these acute cases was to provide sedative and relaxing modifications through exercise.

In observing these patients as they take part in a league soft ball game, for example, one is impressed with the high degree of concentration and the surprisingly intense effort attained. Many apathetic patients will make an unusual effort while playing these games. Very regressed patients are frequently seen backing up plays, demonstrating an acute though spasmodic orientation in the game. Others are observed to show evidence of appreciation for the good plays of their comrades as well as to criticize faulty plays. The sublimation of antisocial behavior is most evident. In a recent game, a player of the acute ward collided violently with another player, a combative type. It was expected that he would become emotionally upset and assaultive. To the surprise of all, he arose, walked over to the other player, said he was sorry and asked if he was hurt.

An intensive program of physical therapy was attempted for the suicidal type of patients. There were 35 in this group, ranging in chronological age from 35 to 40 years. Sixteen took part in formal types of exercise, such as swimming, calisthenics, and gymnastics, and 17 took part in informal types of exercise, including soft ball, baseball, tennis, bowling, volleyball, codeball. Two did not take part in physical therapy, because of confused, stuporous condition resulting in a disorientation towards these types of activities. During the past 6 months, 8 have been transferred to other wards as a result of their improvement.

The objective for these suicidal cases was to re-establish spirit and morale, and this type of therapy seemed admirably suited for the purpose when considered as a long-range activity. At the beginning, many were antagonistic toward efforts to enlist them into any form of exercise. They were resentful because of their restriction and did not participate. As leagues became organized and many types of activity were included in the general program, some of these patients would request to take part and at present writing all but 2 of these types will take part in calisthenic exercise, many of them showing real interest and spirit; a number have been transferred to another ward and are now making satisfactory adjustment to the more responsible procedures of work.

In observing the conduct of many of these patients over a period of 2 years it appears that the confidence and satisfaction developed through their play activity has become enlarged until it touches and colors many other relationships. Whereas it was necessary formerly to keep these patients locked up and under the closest supervision, they now enjoy considerable freedom; they come to the recreation building daily for exercise, are most co-operative and amenable, and appear to have improved in desirable social striving and morale.

The present set-up at the Veterans' Administration Facility, Perry Point, includes a wide category of formal and informal activities. Under informal activities are provided regulation baseball, regulation volleyball, playground baseball, duckpin and tenpin, bowling, codeball, tetherball, golf, croquet, handball, tennis, shuffleboard, pocket billiards and impromptu games. Under formal activities are included calisthenics, gymnastics and swimming. Attempt is made to provide a suitable type and grade of activity

for the patient's mental, physical and social tolerance. The idea has been to progress the program from the fundamental therapeutic point of interest to effort and in carrying out this plan the aim has been to make the patient feel that the activity is self-imposed and purely voluntary; play is not considered as an end in itself but as an important part of the therapeutic regime of work, rest and recreation.

In conclusion, the writers do not wish to create the impression that physical therapy has been viewed as a panacea. Its many limitations, both as to content and methods, have been apparent in attempts to utilize many and diversified activities nor has physical therapy been employed at this Facility as a purely independent adjuvant. The ideal therapeutic program advocated and carried out has represented a balanced regimen of work, rest and recreation. Attempts are constantly being made to impress patients with the importance of progressing from play activity to the more responsible rôle typified by work, so that they may be assisted in their return to normal responsibility. The importance of utilizing play mechanisms as a distinctive means of elevating the patient's social respect in the direction of more easeful and confident social relationships, which will assist the individual to resume his place in normal society, is being constantly stressed. The physical program has been organized so as to fit most effectively and co-operatively into the regular hospital routine.

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### PHYSICAL THERAPY IN BACKACHE

Meyerding and Pollock<sup>24</sup> believe that backache is not a disease, but may be the symptom of a multiplicity of varying dis-

orders, the elucidation of which frequently presents problems of overwhelming difficulty.

In the backache due to arthritis, they state that generally speaking, conservative measures should receive first consideration, since many, it might almost be said, the majority, of backaches will respond satisfactorily to the simpler methods of treatment and, even if these fail to relieve completely, they very frequently provide a clue as to what should be done subsequently. These authors believe that to urge surgical fusion of a lumbosacral and sacroiliac joint, the seat of hypertrophic changes or well marked arthritis, when no relief has followed the use of a well-fitting lumbosacral or sacroiliac belt, may court an unsatisfactory postoperative result. Again, the absence of any alleviation of the patient's symptoms by routine use of rest and physical therapeutic measures may be the deciding factor in instituting extensive neurologic investigation in an obscure case of backache with sciatica. It will be found that the condition in a vast majority of patients with sacroiliac arthritis will improve with the use of *heat, massage, supportive corsets* and change to a *less strenuous life. Heavy lifting should be avoided.*

It is in the treatment of acute backache that physical therapy produces its most spectacular results. The acutely painful back which is so characteristic a precursor of influenza or smallpox, or follows unaccustomed and prolonged physical effort, such as gardening, forms an excellent example of the efficacy of heat and massage in the cure of low back pain. Fibrositis, myalgia and "facet syndrome" pain all can be grouped together as etiologic factors in acute backache, and each is susceptible of considerable relief by physical therapeutic measures.

These authors believe that for cases in which structural defects and obvious pathologic change are absent, the routine treatment is standardized and successful within a few days. The patients are hospitalized in a *bed* provided *with a lumbar sling and apparatus to apply extension to the lower limbs*. To begin with, 4 to 6 pounds (1.8 to 2.7 kg.) are applied to each lower limb and the patient lies on the lumbar sling in such a manner that the buttocks and lower part of the lumbar spine lie on the canvas support. The weights are increased from time to time if this is found to be necessary. The discomfort is increased, usually, by the hyperextension of the spine and by the unaccustomed pull on the legs; few patients can tolerate this position more than an hour or so at a time during the first 1 or 2 days. It is the writers' custom, therefore, to release the weights or allow the patient to be out of the sling at stated intervals and at meal time. *Codeine* may be necessary for sedation, but after the first few days' administration of this drug, it can be discontinued, as most patients are then able to lie in their slings for hours on end.

Daily or diurnal applications of *heat* are given either by the near *infra-red rays*, since they are more penetrating than the nonluminous sources of heat, or by means of the *fever cabinet* or *Hubbard tank*. *Diathermy* is used occasionally and may be alternated with sessions of other treatment. Choice of sedative or stimulating *massage* depends on the type of each case. If it is one of *fibrositis*, *deep kneading* to dissipate the fibrous nodules is an essential part of the treatment. The large proportion of patients will respond within a week with diminution of pain, loss of muscular spasm, and disappearance of contractural deformity, and most of them

can be dismissed as cured by the tenth day.

In *fractures of the body of the vertebrae or their processes*, maximal relief is obtained by *prolonged rest*, while restitution to normal anatomic contours usually follows hyperextension of the spine, with traction and countertraction. Body *casts* may be applied or the patient may be nursed on a half cast which causes hyperextension of the back. The benefit of the *bivalved cast* lies in the fact that *heat* and gentle sedative *massage* can be applied routinely, whereby muscular relaxation is brought about and a more nearly perfect return to the anatomic norm may be obtained.

In *acute specific infectious diseases of the spine*, treatment is directed against the causal agent by administration of *vaccines*, *eradication of foci* and by *physical therapy* and *dietetic measures* calculated to raise the resistance of the host to the invading organism.

*Congenital lesions per se* should not be the cause of pain or discomfort, and it is the authors' conviction that only in rare instances are they other than developmental curiosities. They do not deny the view, however, that they may render the individual so affected more susceptible to injury. About 10 per cent of cases of congenital spondylolisthesis are asymptomatic and are encountered accidentally during a routine examination. However, about 85 to 90 per cent of patients with spondylolisthesis have as their principal complaint, low backache and some are so disabled that surgical fusion is necessary. Of those who do complain, a large number owe the onset of symptoms to intercurrent injury. Physical therapeutic measures will not alter the architectural conformation of the spine, but *heat*, *massage* and a *chairback brace*, by relieving muscular and ligamentous strain, will enable most patients

who have not been subjected to surgical operation to lead a fairly active and productive existence.

*Incomplete sacralization of 1 or both of the transverse processes of the last lumbar vertebra* may become the seat of traumatic arthritis as the result of multiple microtraumatism. In these cases also, improvements follows the use of **heat, sedative massage** and adequate **immobilization**.

The psychoneurotic group of patients is one of profound interest. To dismiss these patients as neurotic or to classify them among those of constitutionally inadequate personality, is neither fair to the patient nor is it in the spirit of Hippocrates. If it is admitted that a developmental defect in bone may predispose to the occurrence of pain following even slight trauma, should not the clinician be equally ready to extend similar credence to those whose pains are mostly "in their heads"?

The nervous, anxious woman with a *painful coccyx* may obtain, in the experience of these authors, only a temporary respite from pain by surgical methods. The majority, if they receive daily **Sitz baths, encouragement, diathermy, and massage of the coccygeus muscles**, will obtain relief from symptoms.

Not a few of the backaches in youth, as well as those which develop in more advanced years, owe their origin to *faults in posture*. Muscular weakness or imbalance, or habits acquired from occupational activities or physiologic necessity, such as long hours of sitting at desks of poor design or attitudes necessitated by visual handicaps, will cause backache. When these factors continue to act over a long period, they may ultimately lead to structural alterations. Thus, although originally purely functional and capable of voluntary correc-

tion, the latter state of the patients may be one of irremediable deformity.

In this postural form of backache with scoliosis, the physical therapists have a field of endeavor the cultivation of which will yield a harvest rich in arrested and corrected spinal deformities.

**Corrective exercises** to tone up relaxed or overstretched muscle fibers are taught to the patients; they are instructed in the maintenance of **correct posture** and in the importance of following their **daily** courses of **exercises** with an almost religious zeal. **Casts, braces** or even **surgical fusion** may be necessary in advancing or advanced cases, but whether the routine be conservative or surgical, the secret of success lies in the enthusiastic co-operation of teacher and pupil, and a patient's painstaking enthusiasm in the performance of the daily exercises. Photographs and roentgenograms, taken at regular intervals, not only record the progress of improvement, but aid immensely in building up the patient's courage and confidence as he marks off these milestones on the way to cure.

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## PHYSICAL THERAPY IN FRACTURES

**1. Physical Therapy Measures Indicated in Treatment**—Attention is called by Caldwell<sup>25</sup> to the fact that physical therapy has an important place in the treatment of fractures. It accomplishes most, perhaps, in those fractures which intersect joints. Unfortunately, however, treatments have been poorly timed and improperly given in many instances, resulting in more harm than good. To be effective, the proper measures of physical therapy must be timed accurately with the changing conditions of repair that are proceeding in and about the injured joint surfaces.

The measures indicated for treatment in the early stage are early, accurate *reduction* to arrest bleeding and limit later callus formation; *splinting*, to immobilize the parts, check hemorrhage and relax muscular spasm; *sedation*, to relieve the pain; *aspiration of the joint* to relieve intra-articular tension; and the application of a *pressure bandage* about the joint when feasible, further to check bleeding and to hasten absorption of the excess of synovial fluid that is being formed. When the foregoing measures have been carried out, the *part* should be *elevated* to reduce congestion and edema. Considerable swelling and pain usually occur for the first 2 or 3 days and during this time no constriction must take place above the site of fracture.

Because the blood supply to cancellous bone is abundant and the spaces are relatively wide, repair of fractures near the joints proceeds more rapidly than when they occur in the shaft. There is some deposition of calcium and formation of early callus, beginning about the second week and continuing for 2 or 3 weeks, but there is seldom any roentgenologic evidence of this new bone formation and calcification until several weeks later. Judgment as to the amount of motion and strain to be thrown onto this newly formed callus must, therefore, be guided by general knowledge of the pathologic changes together with the symptoms of gradually disappearing tenderness and swelling rather than by interpretation of the x-ray shadows.

It is obvious that the care of the fracture must take precedence over the soft tissue injuries which otherwise might be given heat and massage at an earlier date. Administration of diathermy to the splinted parts has proved impractical. Pain and swelling usually diminish after 3 to 7 days and the circulation then can

be improved by *alternately raising and lowering the injured limb for short periods* of time. *Voluntary movements* of the joints distal to the injury that are not included in the splint, may be started at the same time and is a most valuable physical therapy measure. *Alternately contracting and relaxing muscles in the neighborhood of the joint* accomplishes a sort of internal massage that assists the return of venous blood toward the heart, improves lymphatic drainage, thus decreasing edema and retaining the proper tonus in the splinted muscles.

The purpose of heat is to flush the circulation about the joint and throughout the extremity. *Moist heat*, which can be supplied by encasing the limb in thick, moist bath towels, is a very excellent method of improving the blood supply to an injured joint. In the long run, *immersion of the entire limb in a warm bath* for 15 or 20 minutes is probably the simplest and most effective method that can be used. It, moreover, has the virtue of being easily applied in the patient's home.

A most helpful measure of treatment at this period which supplements heat and massage is bandaging of the entire extremity with a smoothly applied, *elastic bandage*. This should be worn only while the part is in active use and dependent and may be removed when the patient lies down. The bandaging prevents excessive edema, swelling, and congestion, thus aids the circulation and is most grateful to the patient.

The last and most important consideration with reference to physical therapy measures is *motion of the injured joint* at about the fourth week when callus is yet soft and not well calcified. Should active or passive movements be used? Active movements are those which are initiated and controlled by

the patient, and are automatically checked when they cause pain. Passive motion, on the other hand, given by the operator, may not always be stopped at the point of pain, and may produce damage. The muscles, weakened from disuse and splinting, rapidly regain strength through voluntary exercise by the patient; they benefit little, if any, by movements, administered by the operator. The patient, when making voluntary movements, will carry them to the point of mildly stretching the adhesions but will always stop short of tearing them because of pain; when a technician employs forced movements, adhesions may be torn, hemorrhage occurs and new fibrous bands are formed. He who learns to initiate and carry out his own joint movements becomes self reliant, gains confidence, and loses fear, whereas one who is treated solely with passive motion becomes dependent upon the physical therapy technician, dreads his treatment, fears the pain, develops resistive movements, and makes poor progress.

This conception of the physical therapy measures that are of real value is a far cry from the racketeering methods all too common today. Week after week of valuable time is lost when patients report every second day for a so-called physical therapy treatment consisting of diathermy or radiant heat applied to the joint for 20 minutes, following by bathing it a few seconds with alcohol and returning it to a splint. Untold harm is done when the patient becomes discouraged and his physician so desperate that he then resorts to the "pump handle" methods of manipulating the joint, with or without an anesthetic.

**2. Fractures of Upper End of Humerus**—In considering this type of fracture, Alldredge and Knight<sup>26</sup> state

that it should be remembered that greater care must be exercised in the treatment of any fracture, dislocation, injury, or disease about the shoulder joint than in any other joint in the body. This is because of the peculiar anatomic make-up of the shoulder girdle. It is well known that the shoulder has a marked tendency to lose abduction and rotation following injury.

The objective in the treatment of these patients then is the early restoration of function. In order to restore function, *early motion* and *massage* are carried out so that immobilization may be dispensed with and the atrophy and changes taking place subsequent to disuse are prevented. Although it is well known that complete immobilization is desirable in order to obtain bony union in fractures in certain regions, this is not the case in fractures in certain other regions. Fractures in the upper end of the humerus seem to be an exception to the rule. Nonunion in this region is almost unheard of, whether there is impaction or not.

It has been pointed out that these fractures frequently occur in old, obese people. It is needless to indicate the advantage of any method whereby plaster is not used. No splint of any type is necessary. Since the patient is elderly, it is desirable to keep him up and active, as recumbency may produce a long train of complications. Hospitalization is not necessary when relaxed motion with massage is carried out. The patient may be completely ambulatory from the time of the injury and for this reason, this method of treatment is the one of choice from an economic standpoint. After a few periods of instruction, the patient may carry on his own treatment largely at home. Pain disappears after a few days and all soreness disappears by the end of



2 or 3 weeks. At this time active motion of the arm may be started and the bandage be discontinued.

The chief advantage to the employment of this method of treatment is that a certain amount of co-operation and intelligence are essential on the part of the patient. Treatment by this method requires most careful observation and direction on the part of the physician in the early days of the treatment. These disadvantages are greatly outweighed by the advantages.

The patient is placed supine and superficial *heat* is applied for about 10 minutes. This is followed by light stroking massage beginning first about the shoulder girdle and shoulder proximal to the site of the fracture. Following *massage*, a pad is placed in the axilla, the arm bound lightly to the side and the forearm placed in a sling. The patient is allowed to become ambulatory immediately. This is repeated daily for the next 3 days without removing the dressing. This period of treatment simply permits the patient to recover from shock and from the immediate pain suffered from the injury. If *gross displacement* is present, such as complete separation of the fragments with overlapping, *manual reduction under anesthesia*, of course, should be carried out. After reduction of the fracture, *massage* and *relaxed motion* are carried on in the usual way.

After the third day the heat and massage are followed by *relaxed motion*. At this time, after heat and massage have been applied, the patient is allowed to stand up. Great care should be exercised in the changing of the position, so that the patient will not experience any discomfort whatsoever.

*Relaxed circumduction* of the shoulder is accomplished by having the patient bend forward while he is stand-

ing with the knees straight and with the hand of the normal arm resting on the table for support.

**3. Sudeck's Atrophy** — In discussing the after-care of fractures, with special reference to delayed union and Sudeck's atrophy, Jordan<sup>27</sup> states that Sudeck lists 3 types of bone atrophy:

1. The "acute bone atrophy" occurring during the period of healing of an injury to an extremity.

2. The "chronic form of bone atrophy" developing from the first form if the primary focus, especially a fracture, is not healed in due time.

3. The "chronic traumatic dystrophy of the limbs" which usually follows apparently insignificant injuries.

According to Sudeck, the original atrophy named for him, or the acute bone atrophy, which is of primary concern in the after-care of fractures, is not an atrophy at all and not a pathologic condition. It should be called *acute collateral transformation* (Umbau), presenting the same features of regeneration as the callus to which it runs parallel also with regard to the time factor. Acute collateral transformation is not only a common occurrence following fractures or any injury in a wide sense (infection of bones, joints and soft tissues, burns), but a regular sequence to every injury of sufficient strength.

While he considers the acute collateral bone transformation (formerly called Sudeck's atrophy) as a regular physiologic reaction of the extremity to trauma, which is not pathologic and does not require treatment, Jordan is convinced from his clinical experience that the mottled appearance in the x-rays, appearing only in a moderate proportion of cases, indicates an undesirable disturbance in the healing process, if not a complication separate from the

original lesion. Acute collateral bone transformation is almost invariably accompanied by pain and insufficiency. He has seen very few cases in which the typical x-ray appearance of the skeleton of the foot was not associated with more or less severe pain and disability on weight-bearing regardless of the condition of the original lesion. As a matter of fact, an original fracture of the tibia may have solidly united without delay, when the first symptoms of pain and disability and positive x-ray findings develop in the foot. Pain and disability last almost as long as the x-rays show signs of decalcification and *vice versa*. Clinically, the appearance of these symptoms is certainly pathologic and requires treatment.

Just how to treat this complication in the after-care of a fracture is a problem not yet satisfactorily solved. **Weight-bearing with adequate walking and other exercises in the unpadded plaster-of-Paris cast** seems to be most effective. Selected orthopedic appliances may give the same **support**, at the same time permitting free access to the extremity for the application of physical therapy. Support, support, and again support is what is really needed during this phase. Whether additional stimuli producing hyperemia have a beneficial effect or not remains to be seen after further careful investigation. The author's experience has shown that some cases heal faster if hyperemia is induced, while in others the healing might have been delayed by application of heat, vascular massage, and the like. At present, there is still doubt as to whether any local stimulation is indicated apart from physiologic weight-bearing, safeguarded by adequate support.

## PHYSICAL THERAPY IN TENDINITIS OF THE SHOULDER

McKenna<sup>28</sup> believes that in the management of either supraspinatus or biceps tendinitis the *most comfortable initial gesture is immobilization*. Place a pad of cotton or felt in the axilla, strap the arm to the side, apply a shoulder cap of adhesive to prevent shoulder girdle action, and suspend the forearm in a sling. Immobilization of the arm should only be continued during the very acute phase. As soon as restful sleep is obtained it should be discontinued.

Physical therapy is helpful. Radiant heat in the form of *infra-red* is most practical and efficient. **Diathermy** or **short wave**, provided the heat rays pass through the affected area, is very efficacious. Indifferent results are often due to faulty application of the plates or bands. **Massage** and **passive motion** should be indulged in as soon as the acute pain has subsided, usually between the seventh and tenth days. **Daily home exercises** are essential as soon as massage is instituted. Arm swinging with the trunk flexed is the easiest to perform; finger climbing with patient standing beside a wall is the next most practical measure. Passive elevation of the arm by a member of the family while the patient is lying on the back is another acceptable method. Until the patient comes to the realization that 50 per cent of the process of rehabilitation is up to his own efforts, and that the cure does not come in a bottle, the turning point in recovery has not been reached.

**Pantendinitis—the frozen shoulder**—is most likely to confuse the clinician unless a very careful history is obtained. The arm is fixed to the side. All mo-

tions at the shoulder have been lost Abduction, a mere 40° to 45°, is accomplished by painful substitutionary movements of the scapula. Frequently there is a notable wasting of the infra-scapular muscle, while the deltoid is atonic, and the forearm muscles flabby Handgrasp is very weak, yet passively there is no dysfunction of the elbow, wrist, or finger joint motion, no gross alteration of the reflexes, nor sensory changes over the peripheral distribution of the radial, ulnar, or median nerves.

Patients with pantendinitis should be hospitalized and subjected to *gradual traction* on the extremity by means of *adhesive plaster*, with the parts suspended by means of weight and pulleys from a *Balkan frame*. On discharge, usually at the end of a fortnight, after-care is persisted with for approximately 3 months. *Daily home exercises* are insisted upon; physical therapy in the form of *baking, massage*, and *stretching* is administered, preferably by the physician, at 2-day intervals, gradually extending it to 3 or 5 days.

### PLAY-EXERCISES FOR HANDICAPPED CHILDREN

Weinmann<sup>29</sup> states that while teaching pre-school children orthopedic gymnastics she observed that very young children are not yet accustomed to concentrate upon any kind of "work." Their interest has to be won and stimulated by inciting their imagination. Children, even very young ones, are able to imitate rather complicated movements, but they soon get tired of repeating them, unless some means are found to make repetition interesting and joyful. The author found it easy to win and hold children's interest by

transforming exercises into play-form or by imitating various actions which the children have seen performed by the adults of their surroundings Imitating work of different craftsmen, copying the gait and movements of animals seen at the farm, in the zoo, or only in picture books, affords many suggestions for play-exercises.

The child at a certain stage likes playing with imaginary toys and handling imaginary tools. Stern, one of the early representatives of this school, speaking about phantasy and play, says ". . . the child touches and handles airy nothings, *c.g.*, in his game with an imaginary ball, which he can carry on with the same engrossing zeal as when he has a real plaything in his hands . . . But yet in this we always find present one real and apparently essential condition and that is the child's own movement in the game." . . . The thing that can be seen, heard, or touched, can be replaced by an imaginary precept, but not so the individual movement. This tendency affords ample means for stimulating the child's play enthusiasm for performing exercises. Thus its interest is increased in the movements, which incites fresh and repeated efforts.

Two ways can be used to impel a child to perform an action. We may say, "Look here, I am sawing wood; holding the wood with this hand and moving the saw with the other one. Let me see if you can do it?" Or, "Have you ever seen a carpenter sawing wood? Will you show me how he does it?" Both methods are of value and may be used alternately but the second method reminds us of another possibility. The imitation of an action performed from memory is usually not an exact reproduction, but often a new combination of actions fulfilling the

purpose as understood by the child; a transformation of the imagined actions. This is called "*indirect imitation*"; the former method, "*direct imitation*."

In the author's opinion it is of value to encourage the child in working out these "transformations" as well as in making suggestions for new exercises of his own. The child likes to prove to itself and others that it can do something worth doing and tastes the joy of seeing others—the adult—following its suggestions. Often it offers good ideas for some new way of doing things, and always enjoys the creative effort.

The author gives examples for actual exercises. She classifies them into "exercises with real toys or tools" and "exercises with imaginary toys or tools," and "impersonating plays."

**Exercises to Strengthen Foot Muscles**—(Flexors and extensors of toes, interossei, tibialis anticus and posticus, peronei, gastrocnemius, soleus):

1. Sitting—Pick up marbles, beads of different sizes, pencils and keys with the toes.

To arouse more interest, a contest may be suggested between the right and the left foot, *i. e.*, which of them picks up more marbles in the same number of turns.

2. Build towers or similar games with wooden blocks with feet, picking up the blocks between the adducted feet.

3. Pick up soft objects with the toes; handkerchiefs, thick towels, stockings, waving them without dropping, passing them from the toes of one foot to the other one.

4. Place a round bottle on the floor and by means of the toes curled downward, roll and push the bottle to and fro on the floor.

5. Lift the bottle between both the adducted and dorsiflexed feet.

6. Put different small objects of different size into a basket, mixing marbles, beads, smaller and larger balls, pencils, keys, bottles, little sandbags, with the child sitting beside the basket on a low stool or chair. The instructor shuts the eyes and has to guess the object the child is picking up with the toes.

7. Among the wooden "educational toys," one is very helpful for the purpose of foot exer-

cises. It consists of a wooden board with holes. Wooden rods (of different colors) have to be put into the holes and wooden balls on the top of the rods. The children love to do this work with their toes and soon improve amazingly in skill and co-ordination of movements.

8. The rods of the same "educational toy" may be used, playing "tenpins" with them. Stand them up on the floor in 2 or 3 rows or in a circle. The child tries to hit as many of them as possible by a ball thrown with both feet.

## POSTURE

According to Cozer,<sup>30</sup> although it is generally believed that correction of posture in children is valuable, there has been little written to prove this current idea.

The White House Conference on Child Health, as reported by Jones, enunciated the attitude of the physicians who were present at the conference. The impression of these men was that:

1. There is an association, perhaps casual, between posture and failure to gain weight.

2. Digestive disturbances may improve with correction of posture where there is no organic lesion.

3. Good posture is affiliated with a general feeling of well-being and alertness.

In attempting to ascertain the effects of treatment for malposture, it was decided to follow those patients who had been treated for a period of 6 months. It was felt that a shorter period of treatment could not be termed as adequate. Consecutive, unselected patients who were referred to the clinic because of poor posture were used in the series. Forty-eight patients were thus studied.

Therapy for these children with poor posture consisted of instruction by demonstration to both parent and child to correct anatomical and functional poise for the particular child involved. Exercises were performed at the clinic weekly or biweekly and daily at home.

These exercises consisted of a group designated to correct any existing deformity as well as to teach the child correct body mechanics.

Is there any relation between the degree of posture improvement obtained and the well-being of the child? To answer this question, it was necessary to compare those cases whose posture improved enormously with those who showed no change from their original malposture. By far the great majority of the children (44) developed good or excellent poise. Only 3 of the 48 patients had an exceptionally marked improvement of posture. In only 1 of the 48 patients was the posture unimproved by training.

It is to be noted that the child whose posture remained unimproved by training made significant gains in height and in weight. If the posture had improved following training, would the gains have been greater? As a conjecture, an answer in the affirmative may be hazarded.

What, then, may be the result of posture correction in children? In the great majority of cases (96 per cent in the present series) the parents will notice improvement in their child physically, mentally, or both.

In this series of cases it was found that for those children whose parents noted a marked benefit of posture correction, measurement revealed greater gains in weight, height, and vital capacity than in the group of children whose parents noted little or no value of the treatment. Whether or not posture training was of any aid to this smaller group that had the lesser rate of growth, etc., is open to question.

Judging from this series of cases, a fairly accurate prognosis may be rendered in children who are being treated for malposture. It is possible to assure the parents that if they and the

child co-operate in the treatment, the parents probably will note an improvement in the well-being of their child.

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## ULTRAVIOLET RADIATION

**Rickets**—According to Park,<sup>31</sup> rickets can be prevented and cured in 2 ways, *i. e.*, (a) by irradiation of the skin with **ultraviolet rays** and (b) by ingestion of **vitamin D**. He asks, how does it happen that the disease yields to 2 methods of treatment which seem so totally dissimilar? The answer is that owing to a device of nature, the 2 lead to the same final result, *i. e.*, the absorption of vitamin D into the blood. The skin is full of 7-dehydrocholesterol. Active ultraviolet rays, impinging on the skin, convert the 7-dehydrocholesterol, which is the provitamin form of D, into the vitamin form. The vitamin is then absorbed into the blood. If vitamin D is fed, it is absorbed from the small intestine. In the former case the vitamin was manufactured on the surface of the body as the result of chemical action of light; in the latter it entered the alimentary tract ready made.

Since the period of greatest susceptibility to rickets is the first months of life, it is important that full dosage of vitamin D be reached early, certainly by the end of the second month. If real difficulties in the administration of **cod-liver oil** arise, it is advisable to turn to one of the other preparations of vitamin D. A real danger in the use of cod-liver oil is that it may cause lipoid pneumonia if it happens to run down the larynx into the lungs or is aspirated after vomiting.

If some form of **activated milk** is used as the antirachitic agent, as already indicated, the dosage is fixed not

by the requirement of the child but by the amount of milk taken. This may or may not be sufficient to prevent rickets. Either metabolized or fortified vitamin D milk will probably supply sufficient vitamin D during the second year. Irradiated milk may be an adequate source of supply, but if doubt exists supplementation is advisable.

According to the author, the rays of ultraviolet light which are active in the cure of rickets lie between 313 and 230  $\mu$ . When the antirachitic power of individual wave lengths was tested by means of the monochromatic illuminator, it was found that the radiation of 313  $\mu$  exerted a slight antirachitic effect, the radiations at 302, 297, 280, 265, and 253  $\mu$  exerted a strong effect, those at 248 and 240  $\mu$  a feeble effect, and those at 237, 220 and 200  $\mu$  no antirachitic power whatever.

Sunlight consists of visible rays varying in length from 380 to 760  $\mu$  (39 per cent), invisible infra-red rays from 760 to 50,000  $\mu$  (60 per cent), those longer than 4000  $\mu$  amounting to only 1 per cent, and invisible ultraviolet rays from 380 to 290  $\mu$  (1 per cent).

The interposition of the atmosphere and the movement of the earth around the sun combine to cause a seasonal variation in both the quantity and the quality of the antirachitic radiations which reach the earth's surface. The reason for this is that if the altitude of the sun is high, the short antirachitic radiations strike the earth more nearly perpendicularly and hence encounter a minimal thickness of atmosphere and sustain a minimal loss through absorption. At best, the energy of the short rays at the extreme end of the spectrum, whether in winter or in summer, is very small. Measurements in Baltimore revealed that the total energy of the solar radiations between 290 and

315  $\mu$  is from 12 to 14 times greater in summer than in winter. It is necessary to think, therefore, of the solar spectrum in the temperate zone as undergoing a periodic expansion and retraction at the ultraviolet end, the expansion reaching its maximum at the summer solstice and the retraction being greatest at the winter solstice.

Diurnal variations in the antirachitic ultraviolet radiations also occur. During the early morning and late afternoon, when the altitude of the sun is low, sunlight does not possess any antirachitic activity. Naturally, the period of the day when sunlight is effective against rickets is longer during the summer than during the winter.

The ultraviolet radiations of the sun may reach the body either directly or as the result of reflection. The reflected rays are known as *sky shine*, the direct rays as *direct shine*. On meeting the atmosphere, the solar radiations active in rickets are in part reflected and scattered. The cause of the reflection is to be found in the minute drops of water floating in the atmosphere. An infant placed in the shade is bathed only in sky shine.

It is important to have some notion of the relative values of sky shine and direct shine as source of antirachitic rays. In Baltimore, in midsummer at noon on clear days the sky shine in the antirachitic range possesses about two-thirds of the value of the corresponding direct shine; in early spring and fall, it has about an equal value, and in winter a greater value. The ultraviolet radiation in sky shine is far more constant than is that of the direct sunshine. Since the reflected ultraviolet rays come from the drops of water in the atmosphere, their intensity may be actually increased by light clouds or haze.

Altitude as well as latitude is important in relationship to the transmissibility of the antirachitic ultraviolet radiations. The higher the altitude, the thinner the covering of atmosphere that absorbs the short radiations.

Foreign particles in the air, such as dust and smoke, act as absorbents of ultraviolet light. The smoke and dust of cities have greatly reduced the amount of ultraviolet light which penetrates to the street.

Both intensity and time factors are concerned with the therapeutic effect of ultraviolet light in rickets. For example, a long exposure to ultraviolet light when little exists may be the equivalent of a short one under more favorable conditions.

Pigmentation of the skin is nature's method of protecting the dermis. Irradiation, if sufficiently intense and prolonged, will cause ulceration of the deeper layers if all pigment is lacking. Radiation is curative of rickets in the negro in spite of the heavy pigmentation. This indicates the superficiality of the seat of action of ultraviolet light. Ultraviolet light can penetrate the living skin of the rabbit a distance of from 1 to 2 mm.

Window glass removes all radiations shorter than 315  $\mu$ . A variety of substitutes for window glass have been developed, some of which transmit 50 per cent or more of the antirachitic radiations. Only if a room was constructed entirely of the special glass and placed where the view was open, *e. g.*, on the top of a high building, so that the sky shine could enter from all sides, would the special glass have a considerable usefulness, but in winter it would have very little even so.

The artificial sources of ultraviolet light are the *quartz mercury-vapor lamp* and the *carbon arc lamp*, both

far richer than the sun's rays. The quartz mercury-vapor lamp gives off an emission of infra-red (52 per cent) comparable to that in solar radiation, a much smaller percentage of visible light (33 per cent), and a wealth of ultraviolet light of wave lengths ranging from 310 to 250  $\mu$ . Twenty-eight per cent of the total energy lies in the ultraviolet and 6 per cent in wave lengths shorter than 290  $\mu$ .

The carbon arc lamps vary in their emissions according as certain metals, *e. g.*, strontium, nickel, cobalt, cerium, fluorine or iron, are incorporated in the carbon either singly or combined. The radiations are strong in the ultraviolet range between 320 and 230  $\mu$  if iron is used; if strontium, in the infra-red.

Park states that in the temperate zone in the summer, sunlight can be relied on to protect against rickets, except in rare instances, provided the child is exposed outdoors. In the winter, sunlight cannot be relied on for protection from rickets. Indeed it is best to regard winter sunshine as almost devoid of antirachitic rays and hence to substitute other methods of protection.

The quartz mercury-vapor lamp is more apt to cause *burns* than the carbon arc lamp. The burns produced by ultraviolet light are, however, exceedingly superficial (sunburn), and the inflammation disappears in a few days. When either lamp is used, the eyes must be protected. Irradiation with ultraviolet lamps is especially valuable in conditions in which vitamin D cannot be absorbed well from the intestine, *e. g.*, obstruction of the bile duct. It also has been used to advantage in the protection and cure of premature babies. The quartz mercury-vapor lamp and the carbon arc lamp may be used to supplement administration of vitamin D.

When the carbon arc lamps are used, a curative effect may be obtained even though no tanning is produced. Obviously, the use of the quartz mercury-vapor lamp and of the carbon arc lamp is contraindicated in blondes who "burn" and do not tan. For such individuals it is better to rely on the administration of vitamin D.

Of the preparations of vitamin D in oil, *cod-liver oil* is still the most economical. *Irradiated milk* is about one-third as economical as metabolized or reinforced milk. In each case the enrichment process adds about 1 cent per quart, so that the vitamin D milks are considerably more expensive in terms of units than is cod-liver oil or the concentrated fish oils. No extra charge is made for vitamin D in canned evaporated milk.

The quartz mercury-vapor lamps and the carbon arc lamps are expensive sources of vitamin D in comparison with cod-liver oil. The quartz mercury-vapor lamp costs more initially but is said to be less expensive to operate. However, these lamps are not necessarily expensive sources if large groups of children can be treated simultaneously, as is possible in institutions. The carbon arc lamps are the ones best suited for the purpose just mentioned.

**Wounds**—In a study of the possibilities of physical medicine in the infective complications of war injuries, Bauwens<sup>32</sup> states that the hostilities have brought about the recognition that all open war-wounds are infected and that the presence of devitalized tissues constitutes an excellent medium for the development of pathogenic organisms. This knowledge, coupled with the appreciation that mobility is also one of the factors conducive to infective complications, has led to the elaboration of

the treatment consisting of débridement and immobilization in plaster-of-Paris splints.

It has been appreciated that many of the powerful disinfectants favored some years ago possess properties that are irritating or devitalizing to tissues. Ultraviolet rays, oxidizing agents, and some dye derivatives must, however, be counted exceptions. Whether the conversion of ergosterol into vitamin D through the agency of ultraviolet rays of 2900 and 3100 A. u. plays any important part in the healing processes locally is a matter for debate. The problem has, however, been brought nearer to solution by Lichtenstein, who working with various types of oil, found that the bactericidal powers of cod-liver oil were in no way enhanced by increasing its vitamin content by adding some halibut-liver oil. At the same time, he found that the bactericidal action of oils was a function of their organic peroxide content. Using Stevens' technic for irradiating cod-liver oil with ultraviolet light, he demonstrated by this means that the organic peroxide content could be raised by 25 per cent, and that this corresponded with an increase in the bactericidal power of this oil. While indicating that the vitamin content plays but a small part, if any, in sterilization of wounds, it opens up a rationale for using irradiated cod-liver oil.

In the case of a *badly infected wound*, this is first cleaned and given a dose of *ultraviolet rays* such as would cause marked blistering of the normal skin and is then dressed with *oxidized cod-liver oil*. If the wound is deep, it is plugged with strips of *varicosan* or some suitable substitute; otherwise the surface is merely dressed with it. After a lapse of 3 to 4 days, the wound is



once more cleaned, but this time, unless showing signs of requiring a further sterilizing dose of ultraviolet rays, it is first sprayed with oxidized cod-liver oil and then given a fourth degree dose of ultraviolet rays. The thin film of oil acts as a filter, cutting out the shorter ultraviolet rays so that the full dose does not reach the tissues. In other words, the short rays are absorbed by the oil, increasing the peroxide content, while the long rays pass on to the tissues to stimulate healing. The dressing may be the same as that previously used, or *cellophane* may be substituted for it if the discharge is not profuse. At this stage it is important that some pressure should be exerted on the healing surfaces. This can be done by a combination of *moulded rubber sponge pads* and *elastic bandages*.

The treatment is repeated every 4 to 6 days, a record of the size of the lesion being taken each time, not out of idle curiosity but for the purpose of detecting when a change of treatment is expedient. The simplest way of doing this is to trace on a piece of cellophane the contour of the ulcer or wound and after estimating its area, to plot a graph of the progress.

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## PSYCHIATRY

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## THE ELECTROENCEPHALOGRAM IN NEUROLOGICAL DIAGNOSIS

*By* JOSEPH HUGHES, M.D.

In the past 5 years the electroencephalogram (E. E. G.) has become established as a useful aid in neurological diagnosis. Each year since 1935, when Berger's work on tumors was confirmed, the clinical usefulness of the study of brain potentials has become established more firmly.

The clinical work to date may be summarized by the statement that an E. E. G. is a reliable test in the diagnosis of epilepsy, encephalitis, meningitis, arachnoiditis and is also capable of revealing the presence of other organic lesions of the cerebral cortex, such as subdural hemorrhage, softenings, tumors, abscesses or porencephaly.

**Technic of Examination**—Electrodes are placed on the patient's scalp and the brain potentials are led off into high gain amplifiers which in turn drive ink writing pens which record the brain potentials. This examination does not inconvenience the patient any more than taking an electrocardiogram. A normal E. E. G. in general is one in which the potentials range from 10 to 30 microvolts in amplitude and have a frequency of from 8 to 30 per second. Abnormalities are registered in terms of potentials whose amplitude is increased and whose frequency is slow. Abnormal potentials range from 50 to 200 microvolts in amplitude and from 1 to 7 per second in rate.

**Clinical Findings**—Epilepsy may give high voltage spikes, slow, 2 to 3, or 6 to 8 per second waves. Spike-wave patterns may be seen in *petit mal* just

preceding an attack, while 6 to 8 per second waves may be observed just preceding a *grand mal* attack. In the intervals between seizures any combination of abnormal waves may be seen and they will be found throughout both hemispheres. Mild cases of *epilepsy* may have their abnormal cortical activity masked by barbiturates or they may have periods in which their cortical activity is normal. It has been observed by Hughes and Cronik that the abnormal electrical activity seen in epileptics disappears after a convulsive seizure. This does not hold for cases of epilepsy of many years' standing. An E. E. G. does not reveal the etiology of the convulsive seizure, it is only capable of showing the increased irritability of the cortex. The electrical records from patients having convulsive seizures from *toxic poisoning* may be similar to those seen from idiopathic epilepsy.

*Encephalitis*, *meningitis* and *arachnoiditis* may give rise to potentials of large amplitude which may vary in rate from 2 to 7 per second, similar to the abnormal potentials found in epilepsy. These will be found in all cortical leads and must be differentiated from epilepsy by the clinical findings.

The E. E. G. has great accuracy in the diagnosis of *tumors* located on the *superior or lateral aspects of the cerebral cortex*. Tumors on the floor of the anterior or middle fossa or deep subcortical lesions will not be detected unless they produce a secondary irritative

effect on the overlying cortical gray matter. The electrical findings characteristic of tumors are high voltage slow waves, which are localized to a given area.

*Tumors of the frontal lobe* may be localized accurately in a very large percentage of cases, even in the absence of any localizing neurological signs. In large and rapidly growing tumors the E. E. G. may show abnormal potentials arising from the side opposite to that of the tumor. When this occurs, it probably arises from the tumor exerting a "*contre coup*" effect, or from invasion of the corpus callosum. As tumors are lo-

cated deeper in the brain substance, the accuracy of the E. E. G. decreases, so that only 20 to 30 per cent of *tumors of the sphenoidal ridge* and about 10 per cent of *pontile angle tumors* will give positive tracings. Intracellar lesions will be missed and tumors of the fourth ventricle and other lesions of the posterior fossa will usually not be identified.

There are many artifacts, such as scalp and eyelid movements that may confuse the interpretation of the E. E. G., so that accuracy of this procedure will depend upon the experience and skill with which the examination is carried out.

## ELECTROSHOCK THERAPY

By LAUREN H. SMITH, B.S., M.D., and DONALD W. HASTINGS, M.D.

In 1938, Cerletti<sup>1</sup> introduced a new method of convulsive therapy by means of electricity. This technic seems to possess certain advantages as compared with the production of convulsions by means of drugs (metrazol, azoman, camphor, etc.):

1. The patient has an amnesia for the individual treatment. There is no period of apprehension or panic as so commonly takes place between the time of metrazol injection and the loss of consciousness.
2. The convulsion is less severe, as a rule, and the danger of fracture and dislocation appears to be less.
3. No drug is introduced.
4. From the administrative point of view, there is no cost involved after the apparatus has been obtained with the exception of time spent by salaried personnel.

**Apparatus**—This is constructed to give variable amounts of alternating currents for measured periods of time in fractions of a second. Ordinary alternating "house" current (110 V) is used. Step-up and step-down transformers, a

vacuum tube timer, and electrodes for application to the head make up the essential features of the machine. The usual currents delivered are in the region of 80 to 150 volts, 100 to 400 milliamperes, flowing for 0.1 to 0.8 seconds. An ohmmeter is used to measure the resistance through the patient's head (average about 600 to 1000 ohms) and an ammeter is employed to measure the milliamperage delivered. Several types of machines are available commercially, but all are constructed on the above principles.

**Technic**—The treatment technic proper consists of the following steps:

1. The patient is placed on a hard, padded treatment table. A pillow or sandbag is placed under the midthoracic segment of the back to produce a moderate hyperextension of the spine. Assistants hold shoulders, hips, and legs.
2. Electrode paste is massaged into the scalp high on the forehead on each side of the head. The electrodes are placed in position. A soft gag is placed between the teeth to protect the tongue and teeth.

3. Resistance in ohms is measured.
4. Treatment current is determined and machine set to deliver the desired voltage and time.
5. Switch is thrown.

**Reaction of the Patient**—This will depend upon whether or not the current has been of convulsive or subconvulsive strength. Three types of reaction may be seen:<sup>2</sup>

1. **"Missed" Convulsion**—The current has been of subconvulsive strength. The patient gives a quick start and is then immediately conscious. He may be slightly dazed but can answer questions and is obviously conscious. He has no memory of the episode.

2. **Equivalent Reaction**—The current has closely approached the convulsive threshold. He gives the same quick start but does not regain consciousness for a period of some seconds to a minute or more. He is in apnea during this period. There may be slight jerkings or spasticity of the extremities. He then slowly rouses during the course of the next 5 to 10 minutes. There is no memory of the treatment. This reaction is considered to be the equivalent of a convulsion.

3. **Grand Mal Reaction**—This is the common type of response. The patient gives the same initial start and then has a latent period of unconsciousness varying from several seconds to 40 or 50 seconds. Then follows a typical epileptic-like seizure with its tonic and clonic phases which on the average lasts about 60 seconds. Then follows a stuporous stage of about 5 minutes, after which the patient begins to slowly rouse. He is usually quite confused for 30 minutes following the convulsion. There is, again, no memory of the treatment. The patient is rarely incontinent, nor has any male patient been observed to ejaculate.

**Preparation of the Patient**—For the individual treatment this is simple. Breakfast is skipped before the treatment is given. Sedatives are avoided for at least 24 hours before therapy because larger currents then must be employed to convulse the patient. False teeth or bridges are removed in advance.

The studies done on the patient consist of a careful physical and neurological examination to rule out organic disease. The routine laboratory studies are performed. In addition, the following studies are made:

1. **Electrocardiogram**—This rules out abnormalities of conduction which may have been overlooked clinically.

2. **Lateral x-rays of spine**, with particular reference to the thoracic segment. This serves 2 purposes: (a) to give a norm by which to compare subsequent plates, and (b) to help evaluate the patient by ruling out bone disease such as arthritic change, which would make the possibility of fracture more likely.

The electrocardiogram is not repeated routinely during the course of therapy. The lateral x-rays of the spine are repeated routinely after every 5 treatments whether or not the patient complains of pain. X-rays are taken of any region in which the patient complains of pain referable to a bony region following treatment. The rule is: "When the patient complains of post-treatment pain, always x-ray."

**Number of Treatments**—This varies considerably. If the patient has received 15 to 20 convulsions without benefit, the treatment may be stopped and regarded as being a failure. In fact, most patients who recover under the treatments show good results by the eighth convulsion.

**Contraindications to Treatment by this Method may be Outlined as follows:**

1. Organic brain disease.

2. Advanced generalized arteriosclerosis.

3. Advanced heart disease, regardless of etiology. The history of coronary disease precludes treatment.

4. Tuberculous lesions, active or "healed."

5. Malignancy, active or "cured."

6. Thrombophlebitis, acute or chronic.

7. Bone disease.

Any other condition which the clinician regards as presenting a hazard also must be seriously weighed and considered. It will be noted that the age of the patient was not mentioned as being a contraindication. If the elderly patient can qualify under the previously mentioned physical standards, treatment often can be given. To date, the writers have treated 3 patients (with good results) of 72, 73 and 74 years, respectively.

The types of illness treated have been limited mainly to the following: (1) Manic-depressive psychoses, all types and (2) involutional psychoses, all types. The schizophrenic psychoses seem to respond poorly or not at all and insulin shock still seems to be the treatment of choice. Several psychoneurotic patients have been treated but with very mediocre results.

**Complications**—The complications encountered may be several, although by and large they are few in number. The most important are:

1. **Fractures**—Of 90 patients treated to date (by the writers) there have been 4 cases of compression fracture of a thoracic vertebral body. All of these were asymptomatic and discovered by routine x-rays. If routine plates are not taken, most vertebral fractures will be missed. There has been 1 case of an avulsion fracture of the greater tuberosity of a humerus. This gives a fracture rate of about 5 per cent to date. In the

writers' hands these fractures have all occurred in healthy young people.

2. **Dislocations**—Two instances of dislocated shoulder and several cases of dislocated jaw have been seen.

3. **Death**—There are no cases of death reported to the best of the writers' knowledge.

4. **Memory Defect**—This phenomenon is not infrequent and may last for several days after treatment. It is a spotty defect and consists of some inability to recall proper names, the forgetting of incidents, etc. It is a defect into which the patient has insight and he may complain of it. Several cases have been observed in which this memory defect lasted several weeks. No cases have been seen in which there has been lasting difficulty of this type.

5. **Muscle Soreness**—This is not uncommon, especially after the first several convulsions. It is of importance mainly in that it may be confused with fracture. In case of any doubt, x-ray studies should be made.

6. **Headache**—Is not frequent but may occur. It is transient and readily controlled by acetylsalicylic acid.

7. **Nausea and Vomiting**—Is, again, not frequent. It seems to be more frequent if the patient does not remain in bed for several hours after treatment.

**Recurrences**—In *involutional melancholia* there seems to be a remission rate of about 65 per cent. In *manic-depressive psychosis*, depressed phase, the rate is about 80 per cent, and in the manic phase, approximately the same remission rate holds. *Schizophrenics* appear to be little benefited by this convulsive method. To date, there has been a relapse rate of approximately 10 per cent in all the groups treated.

**Summary**—A new method of producing therapeutic convulsions has been

introduced. After brief experience with it, the results seem to be about the same as those produced by the older convulsive agents, but with less danger and much less discomfort to the patient. If

further experience with it bears out the preceding statement, the electroshock method will undoubtedly replace the several drugs now used in this type of shock therapy.

## INSULIN SHOCK THERAPY IN SCHIZOPHRENIA

By FRANCIS J. BRACELAND, A.B., M.D., and THURSTON D. RIVERS, M.D.

The introduction of insulin shock as a therapeutic method in the treatment of schizophrenia was the signal for the appearance of a plethora of other methods of attack. One by one they were introduced and in some cases, extravagant and unwarranted claims were made for them, then just as readily discontinued. Among the few remaining methods used in the larger American clinics, insulin shock is still the method of choice in the treatment of schizophrenia. Electrical shock has been the most recent method examined, but, fortunately, it was in the hands of most competent observers and they found that while it was almost specific for some forms of mental disease, used alone, it was of little value in schizophrenia.

In the present state of world chaos, dependence must be placed almost entirely upon reports from American clinics because the situation in war-torn countries is complicated not only by a lack of workers who can engage in this work, but also by a lack of large quantities of sugar which, of course, are necessary when working with insulin.

There have been many changes in the technic of insulin therapy since Sakel's first published reports. Sakel himself made the first modifications in the treatment by his so-called "phase method." Tyler and Ziskind<sup>3</sup> report that in experimental animals hypoglycemia reaches its lowest level from 20 to 60 minutes

and remains there with minor fluctuations according to the amount of insulin given. Independent of the hypoglycemia, there occur certain clinical symptoms indicative of a progressive loss of function in a phylogenetic order from the higher cortical areas to the lower or medullary centers. By means of wide clinical experience, it was determined that insulin was most efficacious about 2 hours after its administration in the treatment of schizophrenia. The optimum number of treatments varies, of course, with the need of each individual patient. Fifty treatments may be considered an average number under ordinary circumstances.

The daily dose of insulin is progressively increased until stupor results. The facility with which the dosage of insulin is judged comes with clinical experience and there can be no rule of thumb laid down concerning it. Many of the distressing side-effects and complications which arise during the course of the treatment are now much better understood. *Sialorrhea, hunger pains, excessive bronchial secretion and hypermotility of the gastrointestinal tract* may be lessened by the judicious use of *atropine* in physiological doses. Two types of convulsion may occur as complicating factors, and it would be well to mention them at this point. The *early convulsion*, which occurs at the time of the onset of stupor or shortly before

or after it, is an unpredictable complication. It need not be considered an indication for interruption of the treatment. On the other hand, the *late convulsion* occurring after about 1½ or 2 hours of stupor is more important. It is frequently therapeutically beneficial, but it is not sought—rather it is considered a definite indication for the termination of stupor. Failure to terminate the stupor at this time is likely to result in a prolonged stupor. The use of *thiamin chloride* in 1-grain (60-mg.) doses has been of value in prevention of the first type of convulsion mentioned, while the latter type sometimes may be prevented by the timely use of a *hypertonic solution of polysaccharides*. The termination of *hypoglycemic stupor* is brought about by the intravenous administration of 1½ ounces (50 cc.) of 25 per cent *glucose*, or by the administration of the same dose by gavage. The intravenous route is the method of choice because by it delay in absorption and the possibility of pulmonary complications is avoided. The amount of glucose needed depends upon the insulin dosage and roughly 30 grains (2 Gm.) of glucose per unit of insulin is considered sufficient. *Hypochloremia* due to excessive sweating may be prevented by the prophylactic use of *sodium chloride*.

Perhaps the most serious complication encountered in the use of insulin shock therapy is prolonged nonhypoglycemic *coma*. This is a state characterized by stupor or coma, normal blood sugar or hypoglycemia and a persistence of many abnormal neurological signs and physiological deviations. Most of the reported mortality and morbidity of shock therapy is due to this. Peculiarly enough, definite improvement is noted in patients who survive a short period of "prolonged stupor." The satisfactory handling of this situation requires: (1) Cere-

bral dehydration, (2) restoration of the acid-base balance; and, (3) the provision of adequate oxygen supply.

Some clinicians have advocated the use of intravenous insulin. This has its advantages and its disadvantages. One advantage, of course, would be that a much smaller dose of insulin, even 50 per cent is required to produce the desired effect. This is important, because the question of direct toxic effect upon the tissues by large doses of insulin has been raised by the neuropathologists. The disadvantage of the intravenous route lies in the difficulty in estimating the margin of safety in insulin dosage, the rapidity of its effect and the transient period of its activity.

It is possible to combine other forms of shock therapy with insulin shock in the treatment of schizophrenia. If controllable convulsion is desired, it may be obtained by means of *metrazol* or *electric shock* several hours after insulin stupor has begun. In this manner, the untoward effects of the convulsion can be ameliorated.

At the Pennsylvania Hospital for Mental and Nervous Diseases, insulin continues to be regarded as a highly satisfactory method of treatment in schizophrenia. In 125 cases reported by Bond<sup>4</sup> in 1940, there was no neurological evidence of any brain damage. Memory, intelligence and initiative, by psychological testing and by observation, seemed to be as good after shock as they were before. No fatalities occurred in insulin shock patients observed by the writers since the inception of this treatment in 1936.

Statistically, the writers' results compare favorably with those of Ross,<sup>5</sup> who reported on the results in all cases treated in the New York hospitals. His figures for patients recovered or much improved at time of discharge, after 1 year and

after 2 years, are respectively 40 per cent, 29 per cent, 27 per cent; the writers' figures are 51 per cent, 36 per cent, and 29 per cent. It is very probable that when this year's figures are assembled the results will even be better than those given above. All of the Pennsylvania Hospital results have been checked against control cases. When compared with the control cases, the insulin results are most encouraging. In 156 control cases of schizophrenia who were not given specific treatment and who were followed for a period of 5 years, the recovery rate at the time of discharge was only 0.038 per cent. This rose to 16 per cent at the end of the first year and remained at that level for the second and fifth years. Thus at the time of discharge, the percentage difference between insulin and control patients was 51 per cent and 4 per cent. At the end of 2 years it was 29 per cent and 16 per cent. It is possible that the percentages in the treated cases, if watched for 5 years, will more nearly approximate the 16 per cent, but present indications do not point in that direction.

One point which would be in favor of insulin treatment would be that in the patients who recovered under insulin treatment, 95 per cent left the hospital within 1 month after treatment had been stopped, whereas the untreated cases had to wait from 1 to 3 years for improvement.

**Theories of Physiological Action of Shock Therapy**—Among the theories advanced to explain the physiological action of the shock therapies (insulin hypoglycemia, metrazol, severe anoxia, histamine shock, electrical convulsion, fever, prolonged sleep, etc.) in the treatment of the psychoses, the most important are those of Gerard, Himwich and Gellhorn. The first 2 deal primarily

with the possible changes in neuron metabolism, wherever these may be occurring, while the last regards the important site of action of the treatments as the autonomic centers in the hypothalamus. The first 2 theories therefore might be considered possibly complementary to the last, although Gerard emphasizes the cerebral cortex as the site of the remedial action of the changes in cell metabolism.

The neurons of the brain require a relatively large continuous supply of energy for their proper functioning and depend for this supply on the functioning of the oxidation mechanisms which deal with the burning of foodstuffs (presumably mainly glucose) in the cells. Since there is an insignificant storage of oxygen in the brain cells and only a small store of carbohydrate (glycogen), the brain depends almost immediately for its functioning on a continuous supply of oxygenated blood and somewhat less immediately on the supply of glucose delivered to it by the blood.

Gerard explains the current shock therapies in terms of production of an increase in the oxidation or respiration of the brain, induced directly or on the rebound, as the shock is terminated. The evidence for this consists partly in the demonstration of increased electrical activity of the brain in the initial stages of a treatment, although this and the oxygen consumption of the brain decrease markedly as the depth of a treatment progresses (*e. g.*, as the hypoglycemia or anoxia continues to become deeper); and in the appearance of a rebound electrical overactivity when the procedure is terminated (*e. g.*, on the administration of glucose in hypoglycemia or readmission of oxygenated blood to the brain in cerebral anemia). An increase in cortical excitability to incoming impulses has also been shown



upon "going into" and "coming out of" deep insulin hypoglycemia. The theory implies that there is probably, though not necessarily, something wrong with the oxidation mechanisms in the brain of the psychotic\* and this is somewhat borne out by the unusual resistance of dementia precox patients to thyroid administration (Hoskins). Further evidence for this view lies in the fact that some patients are aided by thyroid administration (which increases dehydrogenase enzyme concentrations in the brain); and that pyocyanin, methylene blue, and thionine, which are known stimulants to brain respiration *in vitro*, and have been injected into schizophrenic patients on the basis of the above theory, often strikingly produce periods of lucidity, although they do not seem to provide permanent relief.

Himwich and his collaborators had found that an apparently constant feature of the insulin and metrazol shock therapy was a decrease in the oxidation rate of the brain. (This refers, of course, to a decrease during the actual shock and does not negate the possibility of rebound increase later.) With *insulin*, the reduced respiratory rate (found by measuring the cerebral arteriovenous O<sub>2</sub> and glucose differences, and blood flow) would be due to a shortage of fuel in the brain, due to insufficient glucose in the blood to the brain; in *metrazol*, the asphyxia produced by the severe convulsions hampering the breathing movements, reduces the oxygen available to the brain from the blood for a short period. (See later.) It was hypothesized, thus, that an essential feature of these shock therapies involved in the production of a cure was a depression

of the brain metabolism, or an "anoxia" of the brain. On the basis of this, nitrogen convulsive therapy was instituted in some schizophrenic patients. In this procedure, inhalation of pure nitrogen for several minutes produces a severe anoxemia, and consequently convulsions, which resemble those seen in insulin although they occur in a more rapid and intense sequence. Although some success is claimed for this method, most clinics have discontinued it.

Recently, however, the convulsions (and the asphyxia?) attendant on metrazol shock have been reduced by the use of paralyzants such as *curare* or *erythroidin* with no apparent decrease in the effectiveness of the treatment. Also, the striking electrical changes in the brain which occur with metrazol occur just as well when anoxemia has been eliminated, while brain circulation is apparently not diminished. Consequently, it seems possible that metrazol shock effect on the brain may not help because it produces asphyxia but for other reasons. (This, of course, does not exclude an action of metrazol on brain respiration itself.) Further use of paralyzants with metrazol therapy may help decide this point.

Gellhorn has shown that the various therapies used produce an excitation of the autonomic nervous centers in the brain. Metrazol, anoxia, and fever, for example, produce an increased activity of the sympathetic-adrenal system and of the parasympathetic-vagal system (causing greater insulin secretion) while amytal produces only the former. Emotional activity (noise or struggling in rats) also produced stimulation of both systems. Because many psychotic patients show abnormally low responsive autonomic reflexes, because a severe emotional strain (such as danger to life) may sometimes cause remissions in pa-

\* Whether such an altered metabolism resulted originally in these patients from psychological occurrences, or primarily from "organic" disturbances, or both, is another matter.

tients, and because of the autonomic effects of the therapies, Gellhorn believes that the success of the treatment depends primarily on a stimulation of the autonomic centers of the brains of these patients, in whom he assumes there is malfunction of these centers. He has found further that the blood of manic-depressive patients may contain an abnormally high amount of insulin-like material, suggesting an overactive parasympathetic-vagal system in these individuals.

It should be noted, however, that Gellhorn could get stimulation of the autonomic system with doses of metrazol insufficient to produce convulsions, while it is known clinically that such subconvulsive doses have no remedial effect. While the autonomic effects described by Gellhorn are undoubtedly real, this does not mean necessarily that this is the primary desideratum of the treatments, for many profound and concomitant changes occur, as described, in the cortex and other brain regions as well. For example, the low reactivity of the schizophrenic autonomic system merely may be coincident with a general observed depression of all brain functions.

However, no one of the single theories as they are stated generally can adequately cover the explanation of the action of the treatments. For example, clinicians have observed that the more convulsive type therapies, *e. g.*, metrazol, seem to benefit depressed patients, while insulin hypoglycemia benefits schizophrenics. Obviously, the action of the various treatments is not the same. While no apparent increase can be found in the oxygen uptake of the brain of cured patients, thus arguing against Gerard's theory of an increased respiration in these, nevertheless it is possible that new alternate cell oxidative mechanisms have been released by the treat-

ment in such patients—for the kind as well as the rate of oxidation is probably also important. Finally, for each treatment, added special features may contribute to making them curative. For example, it has been suggested by Elliott (unpublished) that the disappearance of glycogen in the Nissl granules of the neurons during insulin hypoglycemia, may cause alterations in cell structure which might be important.\*

As a sign of the times it is interesting to note that McGregor and Sandison,<sup>6</sup> working in wartime England where sugar is rationed, have been forced to make many modifications in treatment. In the ordinary method of treatment, the patients required about 1 pound of sugar a day. This is greatly in excess of the government allowance. As a result, they have been giving a potato soup to reduce the amount of glucose given by mouth and found it to be highly satisfactory. The potatoes are mashed and mixed into a thin gruel with milk and water and each patient is given a pint (500 cc.) of the mixture. Following this, the patient is allowed a sweetened drink from his sugar ration. The method has been found highly satisfactory for this time of stress, but of course, it cannot compare with the intravenous method whenever that can be utilized. In the evening, potatoes are again substituted for the sweetened drink. Thus, the carbohydrate intake is adequate, late comas were avoided and the patients are kept to their allowance of 8 ounces (240 Gm.) of sugar weekly. Peculiarly enough, these investigators, driven by necessity, have made other interesting observations. To conserve insulin they use the intravenous route and often have seen blood sugar levels of 9 and 10 mg.  $\frac{1}{2}$

\* The authors are indebted to Dr. Ben Libet for his help in the above discussion.

hour after the intravenous injection of insulin, yet the patient was well and talkative. Apparently, the sugar can be entirely removed from the blood without signs of ill-effects and until the

brain glycogen falls, coma does not occur. They feel that the coma produced by intravenous insulin is in general much better and that there is less likelihood of after-shock in this method.

## MIGRAINE HEADACHE

By HAROLD D. PALMER, M.D.

**Phenomena of the Migraine Episode**—These phenomena, attributable in origin to some deeply rooted intrinsic or hereditary predisposition, having as their demonstrable pathology the periodic disruption of vasomotor balance and characterized by excruciating headache, nausea and vomiting, have baffled medical scientists for generations. Review of a vast literature on the subject, study of the recent physiological investigations of the disorder, and long experience with the problem have led to the conclusion on the part of the writer that migraine is a total tissue ailment or toxemia which interferes with cellular metabolism and ultimately disrupts the vasomotor control. Whether this total disorder (probably allergic) of which the headache is only the most distressing manifestation, is cumulative and eventually overflows in the form of headache, or whether it represents a static, but constant, allergic charge which is set off by alterations in the sympathetic nervous system accompanying emotional stress or nervous tension cannot be positively known at this time.

**Advances in the Field of Migraine Research**—During the past few years these advances have taken 6 distinct lines: (1) The study of allergy, especially as related to food substances; (2) a study of the mechanism of headache, with special reference to the sympathetic nervous system and vasomotor

phenomena; (3) a study of endocrine factors both as direct and as contributory causes; (4) the development of more or less specific remedies of which ergotamine tartrate is the most widely used; (5) the introduction of surgical procedures intended to control the pain by rendering insensitive certain local areas of the scalp and face and to control the vascular changes by ligation of cranial vessels; (6) treatment by vitamin B<sub>1</sub> injections and various combinations of the vitamin B complex administered orally.

1. **Allergic Theory**—This is important in any concept of the cause of migraine. Scarcely any patient suffering from this disorder fails to list a series of substances which he believes to be a direct cause of or substantially contributory to his migrainous troubles. In the writer's experience, the most common offenders are seafoods, milk, eggs, cheese, mushrooms, beer, rye whisky, wheat, chocolate and strawberries. In the same way, many patients have listed other apparent causative factors, such as constipation, emotional shock, nervous strain, fatigue, exposure to wind and blinding sunlight. One of the best summaries of the relationship of allergy and migraine is that by Hartsock and McGurl.<sup>7</sup> They expressed the belief that the inherited tendency to migraine is definite. Edema and spasm of the smooth muscles, the chief characteristic of allergy, could read-

ily explain the symptoms of migraine. Furthermore, many patients have observed their own attacks sufficiently to be able to trace the origin to the ingestion of certain foods. The portal of entry is undoubtedly the gastrointestinal tract. Certain disturbances of the gastrointestinal tract would permit absorption of the offending protein molecule more readily than others, and these conditions are more apt to be present when the patient is fatigued or emotionally upset. The migraine syndrome has also been observed to have a direct relation to mechanical duodenal stasis, and some relief has been obtained by its correction. Hartsock and McGurl stated that 30 per cent of patients with migraine secure complete relief so long as they avoid the allergens to which they are sensitive; in this group are included only patients who find the routine sufficiently easy to permit complete co-operation in following instructions. Some benefit is obtained by 45 per cent of patients; this heterogeneous group secures partial relief, *i. e.*, a decrease in the frequency or severity of the attacks or both; 25 per cent fail to respond to specific diets for control of allergy.

Wide experience in testing for allergens has shown that there is no strict agreement between the allergic reactions to food known to the patient by experience and the findings in cutaneous tests. Tuft expressed the belief that cutaneous tests properly carried out and correctly interpreted may be of great value in many cases. However, the cutaneous reactions to foods, as compared with those to other types of allergens, may be slight, or even negative, in cases in which a definite clinical reaction to these foods is obtained.

Foster Kennedy found that 69 per cent of 63 patients with "allergic headache" improved when on a restricted

diet. Winkelman and Moore consider that allergy is under parasympathetic control, and stated the belief that migraine headache is due to localized edema of the brain resulting from allergic sensitivity to foods and that the mechanism is similar to that of asthma. Emotional factors may cause the autonomic nervous system to augment the existing allergic reaction. Vaughn<sup>8</sup> and Rowe, recognized authorities in the field of allergy, stated that the relationship of allergy and migraine is clear-cut; both authors cited striking improvements with carefully managed diets for relief of allergy. Földes has devised an "anti-retentional" diet largely on the theory of dehydration. The diet is rich in protein and restricted in carbohydrates, with a moderate allowance of fat. Moderate limitation of salt, restriction of liquids and the use of laxatives are also recommended. He reported marked improvement in patients with migraine and suggested the "*antiretentional*" diet as a *diagnostic test* for migraine.

**2. Mechanism of Headache** — The types of migraine have been studied by Graham and Wolff and Wolff and Sutherland.<sup>9</sup> The actual mechanics of the *vasomotor system* have been examined during migraine headache, and are at least partially understood. The data show that the pain in migraine is due to the stretch of relaxed arterial walls. The termination of a migraine headache by ergotamine tartrate and by other vasoconstricting substances parallels a decline in the amplitude of pulsations of certain cranial arteries. Ergotamine tartrate produces a decrease of as high as 84 per cent and an average decrease of 50 per cent in the amplitude of pulsations of the temporal arteries when administered during a migrainous headache. There is a direct relationship between the amplitude of pulsation of the cranial

arteries and the severity of the headache. Graham and Wolff concluded that migraine is an expression of dysfunction of the cranial vascular bed, probably dilation of certain branches of the external carotid artery. They did not venture a theory as to the cause of the process. Fay showed that stretch of the cerebral vascular tree produced headache and that dehydration (by means of reduced carbohydrate intake and restriction of fluids), brought about some relief. Fay expressed the belief that there is an ischemic, as well as a hyperemic, stretch and that both processes may give rise to headache.

Study of the *blood-vessel* changes in response to histamine administration has added greatly to knowledge of the mechanics of headache. The recent work of Horton, MacLean and Craig<sup>10</sup> on vasomotor headache related to histamine accumulation has opened a new possibility in the differential diagnosis of various types of headache. Treatment by means of histamine desensitization, in the types shown to be due to histamine accumulation, has been successful. The *diagnostic study* consists of the observation of the patient's reaction to subcutaneous administration of  $\frac{1}{200}$  to  $\frac{1}{120}$  grain (0.3 to 0.5 mg.) of histamine phosphate. The production of severe, throbbing headache similar to the type developing spontaneously in the patient is interpreted as an indication that the patient's episodes of headache are derived from histamine accumulation in the tissues. *Treatment* then can be undertaken by means of a gradual histamine desensitization technic with some promise of success. The method is as follows: Subcutaneous doses of  $\frac{1}{1200}$  grain (0.05 mg.) of **histamine phosphate** are given twice daily for 2 consecutive days, then on the third day the dose is increased to  $\frac{1}{1000}$  grain (0.066 mg.)

twice daily. This is continued until the fifth day when  $\frac{1}{650}$  grain (0.1 mg.) twice daily is given. The dose is continued at this level for 2 to 3 weeks.

In a recent article by Sutherland and Wolff,<sup>11</sup> a further analysis of the mechanism of headache in migraine, hypertension and fever, indicates that during the migraine attack the amplitude of pulsation of only the scalp arteries is increased and that the amplitude decreases as the headache becomes less intense. They observe that the amplitude of intracranial vascular pulsation does not change as the migraine headache recedes. They find that ergotamine tartrate affects principally the branches of the external carotid arteries. They conclude that the extracranial and possibly the dural arteries and branches of the external carotid artery are the chief contributors to the migraine headache. In another recent contribution on experimental studies in headache, Schumacker, Ray and Wolff<sup>12</sup> indicate that the histamine headache is dependent chiefly upon dilation of the cerebral arteries, principally the large arteries at the base of the brain, including the internal carotid, the vertebral and the basilar artery and the proximal segments of their main branches. Thus, the histamine headache is differentiated not only from the standpoint of clinical symptomatology as described by Horton, MacLean and Craig, but also by carefully performed laboratory studies of the behavior of intracranial and extracranial arterial systems.

**3. Endocrine Factors**—In the field of endocrinology, Timme<sup>13</sup> demonstrated a hypophyseal factor in certain cases of migraine and showed that actual change in the bone or distortion in the region of the sella turcica can be found in a high percentage of cases in migraine. O'Sullivan,<sup>14</sup> in a general discussion of migraine therapy, emphasized the value

of endocrine substances in certain cases. Placental extracts (*emmenin*) and estrogenic hormones (*progynon B*) together with *thyroid* medication and other indicated endocrine replacement or stimulation have proved helpful in a significant number of patients. Glass, Catchpole and McKennon found ovarian deficiency in association with migraine. They demonstrated increased amounts of the follicle-stimulating principle of the anterior pituitary and decreased amounts, or absence, of estrogen in the blood and urine of women with migraine. They reported that administration of *estrogenic substances* was successful in 80 per cent of cases. The theory is that estrogen, which is antagonistic to the follicle-stimulating principle of the anterior pituitary, reduces the dysfunction and brings about normal endocrine balance. Disordered menses became regular with this form of therapy. Relapses occurred after estrogenic therapy was stopped. Administration of a preparation containing the gonadotropic principle from the urine of pregnant women was found to aggravate the headaches. Dunn<sup>15</sup> studied the effects of treatment with estradiol benzoate and testosterone propionate in males suffering from migraine. He found that 2000 R. U. of *estradiol benzoate* succeeded in aborting migraine attacks if administered at the onset of the symptoms. A short series of injections of 5000 R. U. in some cases prevented recurrences of headache for as long as 3 months. Testosterone propionate failed to influence the course of the migraine in males. The rationale in the estrogenic therapies seems to be that these substances, which have the property of inhibiting the production of prolactin A of the anterior lobe of the pituitary, prevent certain disturbances of sympathetic nervous system function and thus foster vasomotor equilibrium. Numerous other contributions

in the past 2 or 3 years have dealt with the success and failure of endocrine therapy.

4. *Specific Treatment*—The introduction in 1935 of *ergotamine tartrate* into general use was followed by reports of success in a high percentage of cases. Lennox and von Storch, Brock and his associates, Soltz and his co-workers, and others have obtained relief in nearly 90 per cent of cases of migraine headaches treated with this substance. Recent statistics have reduced this favorable record to approximately 70 per cent.

Ergotamine tartrate may be given orally, hypodermically, intramuscularly or intravenously. The oral dose generally effective is 2 to 4 tablets of  $\frac{1}{60}$  grain (1 mg.) each. The hypodermic or intramuscular dose is customarily  $\frac{1}{240}$  to  $\frac{1}{120}$  grain (0.25 to 0.5 mg.). There seems to be no special advantage derived from the intravenous method of administration. There is no doubt that prompt and gratifying relief is produced in many cases by the use of this drug. However, pure statistics reporting "relief" are likely to be somewhat misleading and certain limitations of ergotamine tartrate therapy have been discussed by von Storch.<sup>16</sup> In 189 migrainous patients treated with ergotamine tartrate, the most commonly observed accessory symptoms were nausea, vomiting, numbness and tingling of the hands and feet, muscular pains and muscular stiffness. It was recommended that *nausea and vomiting* produced by the drug be relieved by the administration of  $\frac{1}{150}$  to  $\frac{1}{120}$  grain (0.4 to 0.5 mg.) of *atropine sulfate*. Numbness and tingling in the extremities constitute a warning of impending arterial thrombosis only if they are prolonged and accompanied by great pain. Other symptoms, such as choking sensations, globus hystericus, insomnia, restlessness, substernal oppression, pre-

cordial pain and femoral or brachial perivascular pain, occur less frequently and, although somewhat alarming to the patient, appear to constitute hazards of minor character only.

Inhalations of **oxygen** have been recommended for the relief of migraine but wide use of them has not been made. They are thought to be at least an aid in aborting some of the seizures. Drewyer<sup>17</sup> reported considerable success with prolonged oral administration of **chondroitin**, a material extracted from cartilage. The dose used was 4 capsules 3 times daily after meals given over a period of from 6 months to 2 years.

5. **Surgical Treatment**—The surgical procedures which have been used in attempts to relieve migraine are **ligation of the middle meningeal artery, cervicothoracic sympathetic ganglionectomy and trunk resection, injections of alcohol in the supraorbital or infraorbital nerve, removal of the stellate ganglion and section of the trigeminal nerve**. Craig and Critchley cited instances of relief from several of these procedures. Harris<sup>18</sup> reported on the success of **alcohol injection** of the Gasserian ganglion in cases described as "**migrainous neuralgia**." This disorder resembles migraine in that it appears to have a similar hereditary background and the attacks are initiated by many of the same precipitating factors. The pain is persistent, is one-sided and in the anterior of the skull, localized chiefly deep in the eyeball, in the temple and cheek. During the attack there is extreme tenderness in the temporal region. Alcohol injection of the Gasserian ganglion completely relieved 19 out of 29 cases.

6. **Vitamin Treatment**—The **vitamin B** treatment is the result of studies of the migraine episode made by the writer in which certain features stand

out as of particular significance in relation to the toxic manifestations, the vasomotor phenomena and the effectiveness of various therapeutic measures. The following train of events is suggested: (1) The cumulative or premonitory stage (toxemia); (2) the stage of sympathetic imbalance, resulting in cerebral vasodilation (headache); and (3) the stage of elimination (recovery).

It is in the *first phase* of the episode that **oxygen therapy, purgation, vitamin B therapy**, and other measures have their greatest effectiveness. Theoretically, these measures have in common an enforced eliminative or detoxifying action, which may remove from the gastrointestinal tract, the liver, or the tissues certain toxic (allergic?) agents. Theoretically, the subsequent series of events culminating in the headache may thereby be avoided. In all of the author's cases in which treatment with vitamin B is now under way there appear on the record numerous notes as to "threatened attacks" which were aborted in the preliminary stage. The *second stage*, of pain and headache due to cerebral vasodilation, is not as easily reversible. More heroic measures must be attempted and the success of any therapy, except the hypodermic administration of **ergotamine tartrate**, in this phase is in the writer's experience, somewhat limited. The *third*, or eliminative stage, is an obvious one in most cases. In many persons increased output of urine follows the headache, and in others the headache is not terminated until the vomiting has been severe. In a majority of cases, generalized muscular soreness of nearly a day's duration follows the headache. It has been noted that a cathartic and diuretic action, and in some cases a period of sleep, followed administration of **vitamin B<sub>1</sub>** during an attack of migraine.

Of particular interest in relation to the metabolic concept is the work of Peters and others on biochemical disorders associated with vitamin B<sub>1</sub> deficiency. Peters pointed out that the acute symptoms of vitamin B<sub>1</sub> deficiency are often not sufficiently stressed, although the chronic symptoms of true polyneuritis are generally recognized. He observed that pigeons deprived of vitamin B<sub>1</sub> show rapid development, within 24 hours, of symptoms indicating a severe disorder of the nervous system. There is opisthotonos, followed by cartwheel convulsions. Vision is disturbed, and the bird does not respond when a finger is placed before the eye. Exercise, noise or strong light exaggerate the symptoms, whereas rest in a dark, quiet room causes the bird to become quiescent. In the terminal stages of the acute reaction there are failures in regulation of temperature. Peters expressed the belief that the acute symptoms are due to toxic products of vitamin B<sub>1</sub> deficiency, of which the only ones known at present are lactate and pyruvate. Motivated somewhat by the suggestions contained in Peter's work on the biochemistry of vitamin B<sub>1</sub> and largely by the conviction that there exists in patients with migraine a total body toxemia of metabolic origin or the absence or deficiency of an enzyme essential to normal tissue metabolism, the writer made observations on the effect of vitamin B<sub>1</sub> concentrates. For this study a number of patients refractory to all forms of therapy were chosen. No satisfactory results were forthcoming from oral administration alone, but to intramuscular injections of large doses of *thiamin chloride* the response was surprisingly prompt and gratifying.

In cases of severe migraine daily intramuscular injections of synthetic vitamin B<sub>1</sub> (*thiamin chloride*) in doses of

from  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains (30 to 90 mg.) are given for a period of 4 weeks. The dose can be increased or decreased, depending on the severity of the condition and whether or not treatment is begun during a seizure of migraine. After the fourth week,  $\frac{1}{2}$  grain (30 mg.) is given 3 times a week for 2 weeks, and then  $\frac{1}{2}$  grain (30 mg.) is given once or twice a week for 2 months or longer. The dose is increased if attacks of migraine are threatened. If an attempt to terminate an attack is to be made, 2 grains (120 mg.) may be given intramuscularly or intravenously. If given intravenously, the dilution should be 1 cc. of distilled water for each  $\frac{1}{6}$  grain (10 mg.) of thiamin chloride. There is little difference between the response to the intramuscular and that to the intravenous method.

It has been found that the maintenance of a high degree of total vitamin B complex saturation enhances the therapeutic effect. It is the author's custom to give orally average daily doses of  $\frac{5}{6}$  grain (50 mg.) of *nicotinic acid* and  $\frac{1}{3}$  grain (2 mg.) of *riboflavin*. In recent months *nicotinamide* has been substituted for nicotinic acid, but no advantage seems to be derived from the former, except that the skin manifestations of flushing and subjective sensation of heat are eliminated with the nicotinamide. It appears that nicotinamide is no more effective in its therapeutic action than the nicotinic acid. It has become standard in this treatment to give large doses of total *B complex preparations* in addition to the concentrated thiamin chloride, nicotinic acid and riboflavin. These can be given in the form of vitamin B complex capsules or a syrup, the average daily dose being equivalent to 750 I. U. of B<sub>1</sub>, 1000 Sherman units of riboflavin and  $\frac{1}{10}$  grain (6 mg.) of nicotinic acid.



This intensive treatment should be continued for 3 to 6 months, depending upon the reaction of the patient. The method should not be abandoned until it has been given at least a 6 months' trial period.

More than 65 per cent of patients treated (60 cases of severe migraine) have experienced complete relief. Approximately one-half of those patients completely relieved have been able to continue for months free of headache after the termination of the treatment. Only 2 patients have had recurrences and those occurred 10 months after stopping the treatment. Most of the 35 per cent not classified as completely relieved have experienced very substantial improvement, both in reduced frequency and reduced severity of the headaches. The ratio of improvement in this group is better than 10 to 1. In addition to the striking relief from headache, attention should be directed to the general beneficial effects of the treatment. In almost all instances where headache did occur in the course of treatment, the attacks were of less severity or shorter duration and were not accompanied by nausea and vomiting. There was not the "poisoned feeling" which usually accompanied or followed the customary migraine episode. Other somatic effects were increased appetite, improvement in general appearance, gain in weight, improvement in digestion and elimination, and what patients describe as a general "toning up."

**Vitamin B** therapy in migraine is directed at the relief of the underlying toxic, theoretically causative process, rather than at symptomatic relief after the headache has begun. It has been successful, however, in aborting attacks in more than 200 instances and in a large proportion of this number 2 grains (120 mg.) of *thiamin chloride* administered

intramuscularly has terminated the episode within 1 to 2 hours.

The inference from nearly 2 years' evaluation of results with vitamin B therapy is that a certain segment of the migraine problem has to do with some underlying cumulative toxic process which is corrected or rendered innocuous by the large doses of thiamin chloride, together with various combinations of the vitamin B complex. In accord with this conclusion is the fact that many therapeutic methods in the past which have been directed at elimination of body toxemia have proved helpful. Numerous beneficial side-effects of the vitamin B therapy have been mentioned. No theory regarding the corrective action of vitamin B can be proposed at this time. It appears likely, however, that vitamin B has some action in correcting or partially alleviating, or giving impetus toward correction of, the theoretical toxic process which leads to the migraine attack; or, vitamin B may replace a deficient tissue enzyme, and may prevent or check at an early stage the upset of vasomotor control resulting from this deficiency.

**Summary**—Migraine is a disorder having many vagaries and an almost innumerable variety of distressing symptoms. It is doubtful that any single therapeutic attack can be universally successful. Complete relief has been obtained, according to authorities quoted, in 30 per cent of cases by the avoidance of allergens. Reports on the percentage of recoveries obtained by endocrine treatment are many and conflicting. Statistics on symptomatic treatment by ergotamine tartrate show that more than 70 per cent can be relieved after the onset of the attack, and that alarming toxic symptoms are rare. Surgical treatment gives uncertain results,

with accompanying drawbacks. Vitamin B therapy shows to date 65 per cent of cases completely relieved. This method is a recent development and the present percentage tabulation, while encouraging, cannot be taken as final.

## PSYCHOLOGICAL FACTORS IN THE ETIOLOGY AND THERAPY OF MEDICAL CONDITIONS

By LOUIS H. TWYEFFORT, A.M., M.D.

The difficulties inherent in the management of "functional" disorders have been due largely to a somewhat confused idea as to their true etiology on the part of the clinician, and a completely inadequate comprehension on the part of the patient.

Yet the excessive incidence of chronic functional illness in private practice, as well as in long-studied, unhelped, referred cases to general hospitals, indicates in part a fundamental lack of appreciation as to how psychological (emotional) factors can adversely influence the course of disease or how their adequate therapy will effect alleviation<sup>20</sup> of many of these illnesses.

The advances made in recent years by psychiatry in the more exact knowledge of mental processes have been of practical benefit to those internists and psychiatrists who have been willing to collaborate in the study of clinical syndromes. This has led to reiterated emphasis on the need of understanding the "total person" in treating disease processes,<sup>21</sup> which point of view is at the basis of the "psychosomatic" approach to medical problems—made necessary by the fact that in every illness there is both a somatic (physical) and a psychic (emotional; psychological) component, *each* of which should be properly evaluated in relation to the total picture.

**General Considerations**—The etiological factors in disease processes group themselves under 2 general headings: I,

*Physical* (*i. e.*, infectious and toxic agents; chronic inflammation; ageing processes; disturbances in metabolism and bodily chemistry; endocrine and vitamin deficiencies, etc.); and II, *psychological* (emotional conflicts leading to somatic manifestation of organ dysfunctions). Clinically, this differentiation is represented by the common term "organic disease" as contrasted with "functional disorders."

The consensus of opinion of many internists and general practitioners suggests that well over half of their patients present purely functional problems, or symptoms partly dependent on emotional factors despite associated organic findings. The *early* recognition and *adequate* handling of functional disorders thus becomes a medical problem of extreme importance.

### "Functional Disorders" ("Organ Neuroses")

**Definition**—A "functional disorder" may be defined as a disturbance of organ-function without inherent structural pathology which may handicap the individual because of the discomfort engendered or because of impairment in general efficiency. Although a primary "physical" factor may be etiologically active in some cases (*e. g.*, reflex irritation, mechanical pressure from neighboring diseased tissues, etc.), yet the majority of these disorders of function are primarily *psychologically* conditioned.

They represent the somatic manifestations of emotional perturbation. The psychogenic factors are usually complex but can, at least in part, be discovered by appropriate investigation. These emotionally conditioned functional disorders have been rather loosely labelled medically by such terms as "cardiac neuroses"; "gastric neuroses"; "gastrointestinal neuroses," etc. These terms by themselves are unfortunate, since they tend to suggest that the cause of the disturbance lies within the *specific* organ involved. Actually a psychologically conditioned functional disorder ("organ neurosis") is part of a larger disorder involving the entire personality, *i. e.*, it is a part-manifestation of a "neurosis" (or "psychoneurosis") which may in turn be defined as a minor disorder of the functioning of the personality expressing itself in physical and in mental symptoms, chiefly subjective in nature. The major disorders of the personality are the "psychoses."

Depending upon the qualitative disturbance of somatic and/or mental functions, the descriptive psychoneurotic reaction-type will vary. Where the symptomatology is predominantly somatic, the term "functional disorder" or "organ neurosis" is reserved. When the clinical picture is characterized by autonomic nervous system overactivity coupled with expressed feelings of mild apprehension, the appropriate diagnosis may be that of "anxiety state," while the label "anxiety neurosis" applies to similar symptomatology associated with severe attacks of morbid fear or panic. "Neurasthenia" is rather loosely used for those neurotic pictures in which the element of chronic fatigue is the chief complaint. In "conversion hysteria" gross, rather dramatic, physical and mental symptoms are present. In "obsessive-compulsive neurosis" physical symptoms

are usually absent, the complaints are chiefly in the psychological fields of willing and thinking (obsessive thoughts; rituals; compulsive impulses; specific phobias) coupled with very rigid, perfectionistic character traits.

**Etiology**—Since the emotionally-conditioned functional disorders constitute one aspect of the psychoneuroses, their etiology is similar. They represent the somatic reverberations of mental conflict resulting from inability to solve or to adjust to the problems of daily living, because of personality handicaps depending largely upon previous conditioning in childhood and in adolescence. These personality handicaps exist often as incapacitating *personality traits* and *attitudes* of which the individual may be consciously unaware, since they frequently operate on an unconscious level. These personality traits are not necessarily a matter of inheritance. Frequently they are a result of conditioning, especially by parents who through attitudes of overprotection unconsciously foster attitudes of overdependency in the growing child and adolescent, or who through overaggressive or overdominant behavior toward the child give rise in him to attitudes of frank rebellion or to attitudes of unhealthy oversubmissiveness and of pathological inhibition, which poorly equip the individual to deal with the exigencies of adult responsibilities. One of the aims in the specific therapy of these disorders is to bring these personality disabilities to a conscious level where they can be dealt with constructively.

Another major handicap in efficient adjustment to daily living are the many frustrations, which *because* of their personality traits, these individuals incur or are unable to obviate, or to compensate for. Though difficult of proof, it is possible that various "constitutional" factors may enter into the background of

these disorders, such as "hyperirritability" of the individual autonomic nervous system, or an inherent lowered threshold of irritability on the part of certain specific organs (Adler's "organ inferiority" concept). Previous injury, disease, or strain upon an organ system may also play a contributory rôle.

More specifically, functional disorders represent the emotional reaction on the part of certain individuals to life-events which engender within these persons strong feelings of insecurity, of uncertainty, of resentment. Viewed singly, those emotions most frequently operative in the background of functional disturbances are anger, guilt and fear. Their permutations are manifold. These life-events may be in the nature of *acute single events* or "shocks" (disturbances in the family, economic or occupational settings, in the field of sexual, marital or social adjustments, or of religious observances) or they may be represented by *life situations acting chronically* (parental overdominance; incompatible marriage; dire poverty; vocational incompatibility). These emotional perturbations are especially keen when the individual experiences indecision or frustration or is prey to emotional conflicts centering around the demands of instinctual drives (self-preservation; sex; social—herd—requirements), or feels torn between 2 possible courses of action, one of which is usually motivated by strong instinctual pressure.

Thus "functional disorders" and other "neuroses" illustrate that in the etiology of diseases processes factors other than noxious physical agents can be operative,<sup>21</sup> and that chief among these other factors are the dynamic potentialities of the "*personality*" (character; temperament) and of the so-called "*pathogenic environment*" (the events and life-situations to which the individual is exposed).

**Misconceptions**—The term "neurosis," under which general heading "functional illness" must be included, is an unfortunate term, just as is the word "nervousness." Inherent in these words is the thought that these conditions are partly due to an intrinsic affection of the nervous system. This is especially evident in the layman's conception of "nervousness" as a "disease of the nerves" or at least as "due to your nerves being run down," and frequently (with the assistance of certain medical practitioners) he thinks of the associated state of the nervous system as being vaguely comparable to a rundown storage battery which needs to be recharged to function more effectively. A more apt illustration would be to compare the individual suffering from a "neurosis" or a "functional disorder" to a radio whose sound output is garbled by the effects of static. Actually in such an instrument the "tubes" and "wiring" are intact, and of themselves noncontributory to the disturbance. No amount of "doctoring" of the tubes and wiring will set things right. The "pathological" agent resides in the electrical storm engendering the static electricity. Similarly in "functional disorders," the nerves merely carry the impulses, set up by the emotional conflicts, to the various organs which act in turn as "sounding" boards for the emotional "storms" within the personality. Thus, a neurosis may be better characterized as a disease of one's feelings than of one's nerves.

Mistaken in his ideas of etiology, the patient may mislead the physician by insisting that his condition dates from an infection, an operation, an accident, childbirth, or a period of "overwork"—events which he feels have "overtaxed" his nerves.

**Symptomatology**—Anatomically, the site of origin of the emotions may be

looked upon as the hypothalamus, which functions as a sort of "bridge" between psyche and soma. It is here that the chief effector organ of the emotions, the autonomic nervous system, has its origin. Accordingly, emotional perturbation will reflect itself principally in those organs supplied by this division of the nervous system, *i. e.*, (1) those bodily organs containing smooth muscle fibers (chiefly tubular structures, such as the intestinal tract, the cardiovascular tree, the bronchi, the biliary ducts, the genitourinary tract); (2) the secretory elements (glandular tissue: including the endocrine organs, especially the adrenals, thyroid, pancreas, salivary glands, etc.); (3) the skin (smooth muscle fibers and secretory glands); and (4) those components of skeletal muscle having to do with tonus.

**The "Anxiety Syndrome"**—Thus, in response to strong emotion (especially in fear or anger), a definite *syndrome* appears, which may be referred to as the "anxiety syndrome" or "anxiety attack." It may vary in intensity or in terms of the presenting symptoms, depending upon whether there is a predominance of parasympathetic (vagal) or of sympathetic innervation. The exact reason why the autonomic innervations of 1 organ may be affected more readily than those of another organ in different individuals is not yet fully understood.

The chief symptoms which may appear in an "anxiety attack" are excess salivation (or dryness), globus hystericus, epigastric fullness, nausea, vomiting, borborygmi, diarrhea (or constipation), mucus in the stools, anorexia; tachycardia (or bradycardia), palpitations, precordial oppression or discomfort; dyspnea, rapid respiration, sighing, sensation of chest pressure; frequency, polyuria; blushing, flushing, sweating (or

clamminess), pruritus; leukorrhea, menstrual disturbances; transient hypertension; transient hyperglycemia (or hypoglycemia), glycosuria; dizziness, faint feelings, fatigue; blurred vision; insomnia or sleep coupled with frightening dreams; and such general subjective complaints as inability to concentrate, forgetfulness, irritability and specific phobias.<sup>22</sup> (Those apparently contradictory symptoms depend upon the predominance of vagal or sympathetic effects.)

The "anxiety syndrome" is as definite a syndrome as is the eruption of measles, but, unfortunately, is rarely diagnosed by the organically-minded physician.<sup>23</sup> Or if a tentative diagnosis is proffered, those impressions most frequently advanced are "hyperthyroidism," "neurocirculatory asthenia," "syncope," "paroxysmal tachycardia," "disordered action of the heart," "coronary spasm," "gall-bladder attack," "vasomotor instability," "vagotonia" or "sympathicotonia," "autonomic nervous system instability." These impressions all fall short of the true etiological factors, *i. e.*, the fear-producing situation or the basic neurosis which can be established on the basis of positive findings if adequately investigated. The symptomatology of the "medical history" takes on special significance if its rather diversified findings fit together into the scheme of the "anxiety syndrome." If the common origin of the manifold manifestations of anxiety is overlooked, the patient runs the risk of being treated symptomatically for a multiplicity of complaints and frequently ineffectively in terms of improvement, since the true etiological factors remain untackled.

**Reversible and Irreversible Changes; Repressed Emotions and Unconscious Conflicts**—When considering "functional disorders," usually de-

rangements in the function of an organ are thought of which are transient and therefore reversible. As a result of the study of the longitudinal picture of diseases in which emotional factors play an important rôle, it is being increasingly suspected that functional disturbances acting intensively over a *short* period of time, or less intensively over a *long* period of time may play a significant rôle in bringing about structural changes, actual tissue alterations. The original reversible changes have eventually led to irreversible changes.<sup>23</sup> More explicitly, functional spasm in blood-vessels (if acute or if acting over long periods of time) may result in ischemia and eventual necrosis of the area supplied (a possible etiological factor in peptic ulcer). An emotionally induced spasm of a muscular tube such as the esophagus may lead to proximal secondary dilatation; or spasm in the cystic duct, bringing about stagnation in the flow of bile, might play a contributory rôle in stone formation. Similarly deleterious effects would follow in the wake of chronically (emotionally) disturbed glandular (especially endocrine) organs — a possible etiology in certain cases of hyperthyroidism, of diabetes. These “organic” changes would be the last link in a lengthy causal chain, the initial links of which would be constituted by psychogenic disturbances.

In producing those chronic organ tensions which are at the basis of chronic or recurring disturbances of function, thorough psychiatric investigations, and especially the use of that specialized technic of studying the unconscious motivations of personality, *i. e.*, psychoanalysis, have shown that *repressed* emotional conflicts are of major importance. These conflicts which center around fears, aggressive trends, unacceptable wishes, personality inadequacies, etc.,

have been “repressed” into the unconscious, and still operate from that level unbeknown to the individual until uncovered during treatment, after which they can be handled more rationally on a conscious level.<sup>24</sup> The repression of these emotional conflicts was effected because of their being especially distressing to the rest of the personality, or because their solution on a basis of compromise or sublimation was, because of circumstances, originally impossible or undesired. Nevertheless, the emotional energy of these unsolved conflicts, being denied expression in the form of consciously willed action (over the central nervous system), continues to express itself through the wrong channels, *i. e.*, through the autonomic nervous system, with resulting disturbance of the functions of the vegetative organs.

**Differential Diagnosis**—In differentiating between organic pathology and functional (psychogenic) disorders, it must be constantly kept in mind that either type of disorder may use the same anatomical mechanisms. Thus, an organic lesion in the hypothalamus or an emotional storm originating at this same level (Cannon’s “emotional level”) may manifest the same objective and subjective symptoms. In visceral pain (from contraction, overdistention, pulling or pressure upon a viscus), the perceptive mechanism is the same whether these alterations are due to local organic disease or to the overaction of the autonomic nervous system under the stimulus of the emotions. It must also be remembered that anxiety from emotional conflicts expressing itself somatically may *alternate* between several organ systems, presenting somewhat confusing alterations in the clinical picture. If the varied aspects of the “anxiety syndrome” are kept in mind, the oneness of the total picture will not be affected.

Among the most common differential diagnoses which present themselves in considering "functional disorders," or emotionally-determined mild "anxiety states" are the following: incipient hyperthyroidism, very early essential hypertension, hypoglycemia from organic causes, intestinal allergy, carotid sinus syndrome, epilepsy, intracranial mass lesions. Hyperthyroidism and essential hypertension are especially difficult to rule out, since it is felt more and more by a number of investigators that in many instances these 2 disease-processes are themselves largely emotionally determined. It goes without saying that a conscientious history, a thorough physical and neurological examination, adequate chemical and laboratory studies are prerequisites to any differential diagnosis. Nevertheless, an adequate understanding of autonomic nervous system functions, some familiarity with the "anxiety syndrome" and elementary but common-sense psychiatric knowledge, will orient the inquiring physician in the proper direction as he seeks the true origins of a "functional disorder," and will save him from the many useless laboratory investigations which are inflicted upon the patient by clinicians who insist that all disease processes "must be due" to some undiscovered organic pathology.<sup>25</sup>

**Common Clinical Syndromes Frequently Presenting an Emotional Etiology**—As a result of the closer cooperation between internists and psychiatrists in recent years, there have appeared an increasing number of studies of clinical syndromes from a simultaneous physical and psychological point of view. The results of these investigations strongly suggest that emotional factors play a greater etiological or contributory rôle in certain disease processes than had been appreciated. The following

clinical syndromes frequently present important emotional components:

*Gastrointestinal Tract* — Cardio-spasm,<sup>26</sup> pylorospasm, peptic ulcer, spastic bowel, chronic diarrheas, spastic constipation, mucous colitis,<sup>27</sup> and non-specific ulcerative colitis.<sup>28</sup>

*Cardiovascular System*—Essential hypertension,<sup>24</sup> coronary spasm,<sup>25</sup> vasomotor instability.

*Respiratory System*—Chronic rhinorrheas, certain sinus affections, certain cases of bronchial asthma.

*Skin*—Urticaria, eczema, pruritus.

*Endocrine and "Metabolic" Disorders*—Anorexia nervosa, hyperthyroidism, diabetes, rheumatoid arthritis.

In many of these illnesses, it is felt that a number of the structural changes which eventuate are the secondary results of acute or long-sustained emotionally induced physiological dysfunction.

**Experimental Evidence; Experimental Psychophysiology**—Over a considerable period of time there has been amassed an extensive literature on the experimental production of "functional disorders," of emotionally-induced organ dysfunction or emotionally-induced chemical changes, not only in animals, but likewise in the human. In controlled laboratory situations using human subjects, it has been possible to bring about marked variations in blood-pressure readings, heart and respiratory rates. By artificially creating certain emotional states, especially with the aid of hypnosis, it is possible in certain individuals to cause, at will, increase or decrease in basal metabolic readings, and in bodily temperature. Under strong suggestion the motility as well as the secretory functions of the gastrointestinal tract can be significantly altered. Under hypnosis it has been possible to initiate as well as to dispel, at will, attacks of bronchial asthma. In this state of extreme sug-

gestibility it has been possible to alter the menstrual cycle in a number of subjects. Ever since the classical experimentations of Cannon, it has been known that hyperglycemia and glycosuria can be induced experimentally on a basis of strong emotional stimulation. Even leukocyte counts will vary as the result of strong emotion. Electroencephalographic tracings have disclosed that strong emotionally-laden ideational stimuli will give rise to cortical currents similar to those obtained from direct electrical stimulation of these areas. Similarly it is known that muscles will register action currents in response to mere ideas of motion.

Reference has been made to the use of hypnosis in some of these experimental situations. This phenomenon, closely allied to natural sleep, is useful chiefly because of the marked degree of suggestibility which exists during the hypnotic state. At this time an emotion is suggested to the subject by evoking the life situation which would give rise to such an emotion.

**Special Points in History-taking in Observation of Patient Suspected of Functional Disorder**—Many patients suffering from emotionally-induced "functional disorders," or mild "anxiety states" do *not* "look neurotic." Furthermore, since the sources of emotional perturbation are frequently repressed, or if known to the patient, carefully guarded from the scrutiny of those about him, the positive evidence upon which a diagnosis is to be established must usually be obtained in *indirect* fashion.<sup>29</sup> In addition to the customary medical approach (history and laboratory studies), a thorough *personality study* is indicated to enable the physician to understand his patient as a human being rather than as a medical case. Such a psychiatric evaluation of the patient should not be car-

ried out too soon. A thorough study along organic lines of approach should come first, as evidence of proper respect on the part of the physician for the patient's physical symptoms. Too hasty inquiry into emotional factors may lead the patient to fear that the physician regards the symptoms as "just imaginary" and to become rightly incensed, for to the lay mind physical discomfort is only caused either by physical pathology or by "the imagination."

Many significant factors in the patient's history, especially in cases of functional disorders, are liable to escape the attention of the organically-minded general practitioner,<sup>30</sup> especially if his inquiries into the emotional background are limited to the query: "Have you any worries?" and if he is satisfied with a negative answer. This common question is not only inadequate, but actually harmful, since if answered by the patient in the negative, it may frequently hinder the later disclosure of pertinent information on his part, lest his initial denial reflect upon his veracity. The true causes of emotional tension are usually concealed.

**Personality Study**—Significant data pointing to emotional factors operating in the background of an illness are secured more readily by indirect than by direct questioning, or in the form of clues which will be very meaningful to the alert observer. Such data will at times permit an indirect evaluation of unconscious (repressed) attitudes, those chiefly responsible for chronic tension states.

Before any questions are asked, the patient should be allowed to talk spontaneously at some length about his illness. During this time the following especially should be noted: General appearance; use of cosmetics (excess, dyed hair, etc.); volubility; circumstantiality;



presence of neurotic overconcern; obvious neuroticism; bids for sympathy; attitude toward physician or hospital; mood; suspiciousness. With regard to the patient's spontaneous statements—especially “slips” or casual misstatements followed by immediate attempts at correction; omissions (as compared with previous statements); contradictions; sudden recollections of previously “forgotten” (repressed) important experiences; topics not mentioned, avoided or circumvented; topics which the patient spontaneously strongly denies as in no way contributory to his illness.

Findings which would be especially suggestive of pent-up emotional tensions are: harrassed facial expression; obvious muscular tenseness; restlessness; purposeless gestures; tics; close bitten nails; symptomatic excess smoking; increase in tension and embarrassment when questions arouse emotions associated with unconscious or repressed conflicts; violent blushing while making specific denials; episodic stammer while discussing specific subjects.

In the “past medical history,” especially significant is the discovery of long series of previous illnesses, especially if the disease processes appear to have been disturbances of circulation, of secretion or of the muscle tonus of internal organs<sup>31</sup> (*e. g.*, history of blood-pressure fluctuations, of suspected gall-bladder disease, of colitis, of “appendicitis,” of alternating diarrhea and constipation, of menstrual irregularities). Such findings are especially important if several organ-systems appear to have been involved simultaneously.

In the review of the present functioning of the various organ-systems, special note should be taken of the occurrence of any of the symptoms which fit into the “anxiety syndrome” (*vide supra*).

Specific inquiry should be made as to the content of dreams. Anxiety dreams may frequently contain disguised clues to important repressed psychological conflicts, especially where repressed hostile and aggressive trends exist in a superficially placid and submissive individual.

The elicitation of neurotic traits in the childhood history is suggestive, especially the former occurrence of nightmares, somnambulism, enuresis, thumb-sucking, nail-biting—symptoms frequently suggestive of a tense child-parent relationship.

Some appreciation of the early child-parent relationship is of importance, especially parental attitudes of overdominance which engendered feelings of fear or resentment, or of overprotection with resulting feelings of overdependency and subsequent insecurity. Other important lines of investigation center around the following: job and work (satisfaction, conflicts); sexual and marital adjustments (sexual problems are often the result rather than the cause of neurotic trends); social interests (adequate recreational and hobby outlets); religious conflicts; dissatisfactions in terms of life-goal, life ambitions; significant thwarted desires; “caged” feelings. Is the individual living the way he wants to live, or as others expect or insist on his doing?

Feelings of inadequacy caused by attitudes of extreme submissiveness are especially frequent in producing chronic emotional tensions, the tension in part resulting from the inner rebellion at the inability to assert the self.<sup>24</sup> Such attitudes are in many cases the carry-over into adulthood of character traits developed in response to parental attitudes.<sup>20</sup> A patient may give voice to these trends in such statements as: “Father can make me cry by a word”; “I cannot stand up for my own rights”;

"Peace at any price is my motto—I can't take it, can't fight back"; "I react to things inside, though I always hide my feelings."

Naturally, a detailed, accurate *chronological* account of the development of the various symptoms of the illness is of extreme importance, since appearance or exacerbation of symptoms can often be correlated in a time-relationship with specific life events. Yet, taken by themselves, these environmental happenings are etiologically of little importance. They gain their weight only when evaluated together with the individuals' personality,<sup>81</sup> a personality which may have been conditioned in a *special* way to similar experiences in earlier life.

A thorough medical history supplemented by even a fairly superficial personality study, carried out in an attitude of genuine interest toward the patient's problems as a human individual, will almost invariably bring to light material which will make possible the diagnosis of "functional disorder" or of "neurosis" on the basis of *positive* factual evidence,<sup>23</sup> as against the so frequent "functional" diagnosis arrived at solely on the basis of exclusion—"all the studies having proved negative, the patient must be suffering from a psychoneurosis(!)"

A positive diagnosis of "functional disorder" or "psychoneurosis" will make possible the adequate, specific, handling of the emotional factors by adequate psychotherapy and thus hasten convalescence, prevent exacerbations and that tendency toward chronicity and invalidism which characterizes the functional disorder or neurosis in which mere symptomatic treatment is undertaken. Early neuroses are usually seen by the general practitioner some 10 years before they reach the psychiatrist.

The importance of their early treatment is self-evident, before more serious

personality maladjustments become manifest, especially in view of the marked time element required in the therapy of a well-established neurosis.

#### Physician-patient Relationship—

##### (a) *Detrimental Attitudes on Part of Physician*—

It is unfortunate that a great number of patients have developed intensified functional disorders or psychoneuroses because of various medical attitudes to which they have been subjected. Frequently, after endless procedures and laboratory examinations which have revealed no pathology whatsoever, they have been told by an essentially organically-minded physician that there is "nothing wrong at all," that it is "all in their imagination," that they should "forget their troubles and brace up." In other cases, the psychoneurotic patient is put through an endless routine of investigative procedures in the hope that "something will be found," some organic cause, if only one looks long enough or carries out enough tests. In the course of these scientific ordeals minor discrepancies are frequently encountered and clutched at by the physician in his frantic attempt to discover some organic pathology to "explain" the illness, and the blame for the illness becomes attached to such scapegoats as a deviated septum, visceroptosis, a minor uterine displacement, a low-grade urinary infection, some pharyngeal lymphoid tissue, etc. The more varied the tests and the more frequently they are repeated, the more positive does the neurotic patient become in his belief that his illness is unique and undoubtedly serious.

Other attitudes on the part of the physician which may increase the neurotic patient's anxiety are diagnoses made in very general terms, such as being told that he suffers "from a nervous heart," from an "acid condition," from "his nerves," from "acid indiges-

tion," pronouncements which merely restate previous self-observations. Any diagnosis which the neurotic patient cannot clearly understand is apt to aggravate the situation.

No greater harm can ensue to a patient suffering from a functional disorder than that which may result from "exploratory" laparotomies recommended in the hopes that some physical cause for the abdominal symptoms may be discovered. The stage is then set for a scalpel-induced vicious cycle, post-operative symptoms being blamed upon post-operative adhesions, the final outcome of which may be the "gridiron belly." Surgical attempts at intervention in the physiological expression of emotionally-induced disorders, implies little knowledge of the alternation of anxiety symptoms, of the variations in channels of expression. Such therapy may merely shunt the emotional tension into another organ-system, which in a neurotic woman frequently accounts for the history of an appendectomy in her teens, a thyroidectomy in her twenties, a gall-bladder removal in her thirties and a panhysterectomy in the fourth decade. No surgery should ever be undertaken "in the hope of relieving" some functional disorder without a complete preliminary psychiatric examination and evaluation.

**(b) Constructive Attitudes on Part of Physician**—Every patient is entitled to a simple, clear, and frank explanation of *all* the tests and examinations made in connection with his physical complaints, and this applies with equal emphasis to the results of negative studies, which investigations, during his period of suspense, he may have invested with just as ominous implications. Then, too, the patient should be given the opportunity to ask any questions which occur to him, in fact be *urged* to do so. It is sur-

prising how frequently patients harbor misconceptions or make harmful deductions, and the rectification of these unfortunate impressions become matters of definite therapeutic importance.

The most difficult task facing the internist is the interpretation to the patient of the nature of symptoms proven to be of functional or emotionally-determined origin. Since to most lay persons symptoms are either due to physical disease or "due to the imagination," some physicians may hesitate to tell the patient that his symptoms are on a functional basis, since the suffering patient expects something concrete to account for his discomfort, and might be inclined to interpret a suggestion of emotional etiology as implying that the physician suspected "something mentally wrong," or that he was "a mental case."

With some persistence and considerable patience, it may be possible for the internist to give the patient at least some superficial insight into the nature of emotionally-induced symptoms. By simple illustrations it is possible to explain to the patient how such emotions as fear may cause rapid heartbeat; disgust, nausea; anger, a feeling of tension, etc. They may at times then spontaneously connect certain exacerbations of their past symptoms with specific environmental situations which were emotionally laden. Thus, their symptoms may start having a new meaning, a cause for some of them having been uncovered, even though the nature of the cause implies the acceptance of an entirely different concept of illness. With the beginning of understanding or insight formation some symptomatic relief may ensue. For the more deeply rooted emotional causations, however, more intense psychotherapeutic technics are required.

**Treatment of Functional Disorders and of Incipient Neuroses—(a) Gen-**

**eralities**—The general aim of psychotherapy in the functional disorders and in the incipient neuroses (especially the mild "anxiety states" so frequently seen in general practice) centers around assisting the patient gradually to develop an understanding into the meaning of his symptoms and into the nature of his conflicts, whether they be due to situational factors in the environment or to personality shortcomings. Essentially, the aim should be at a re-educational process together with a more adequate emotional development on the part of the patient.

**(b) Rôles of Internist and General Practitioner**—Unless the physician has had considerable experience with the psychological handling of emotional disorders, his field of effectiveness is rather limited. He may succeed in helping the patient to see how certain emotional factors may precipitate or aggravate his symptoms; he may afford the patient considerable relief by permitting him to "talk out" certain of his problems; he may be able to eliminate or correct certain harmful environmental factors; and by calling upon various community agencies, rectify certain distressing situational factors in the home.<sup>21</sup> Beyond this, his responsibilities will evolve around referring the patient for specialized psychiatric help, and one of his most helpful contributions at this point will consist in preparing the patient for such further treatment, by explaining to him the aims of such therapy and simultaneously stressing the time, effort and co-operation required for successful therapy.

**(c) Specific Psychotherapy**—"Major psychotherapy" becomes necessary when the emotional origins of the symptoms spring from deeply repressed conflicts and immature personality trends. Through specialized technics it is possible to bring the repressed psychological conflicts, whose associated emotions are

causing permanent tensions, back to consciousness, thus permitting a constructive conscious solution of the conflict. From their somatic channels, the energies of the repressed conflicts are, as it were, converted into psychic channels where they can be dealt with consciously through the intermediary of speech and volition. When the patient is gradually helped to face harmful tendencies formerly repressed, handicapping attitudes which were largely unconscious, and previously denied personality liabilities, and when there develops a willingness to face critical life-issues instead of sidestepping them, a process of re-education and of personality synthesis then may be attempted.

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## RADIOLOGY

*Edited by* EUGENE P. PENDERGRASS, M.D.

### THE CYCLOTRON

*By* GAYLORD P. HARNWELL, B.S., A.M., Ph.D.

In the past many of the instruments and technics of physics have found applications in the fields of biology and scientific medicine, but it is rare that a field of physics, while still in its infancy, has contributed so greatly to the biological sciences and offered such important future promise as does the field of nuclear physics. The reasons for this unusual situation are twofold. One is that the medical technics involving natural radioactive material and high energy radiation are already well developed and the importance of the vast enhancement of these technics made possible by nuclear studies is immediately evident to radiologists. Secondly, the fields of biological and medical research are ripe for the employment of the radioactive tracer-atom technic which has emerged as a by-product of investigations in nuclear physics.

The past 10 years of the study of the atomic nucleus by physicists have resulted in the opening of 3 new avenues of investigation that are of interest to medicine. The first of these is the development of new intense sources of high energy electromagnetic radiation. This should

supplement and extend the fields of x-ray and gamma-ray studies. The second is the technic of endowing practically all the known chemical elements with the attribute of radioactivity. The importance of this is twofold, for it presents direct therapeutic possibilities heretofore undreamed of and also supplies research medicine with a new ability to trace chemical elements through all the physical and chemical processes taking place in living organisms. Thirdly, the study of the atomic nucleus has uncovered the existence of a hitherto unknown type of elementary particle known as the *neutron*. This is a particle with a mass approximately the same as that of a proton but distinguished from it by having no electric charge. In consequence of its electrical neutrality, its interaction with other atoms is profoundly different from that of the electron or proton and there is reason to believe that its biological effects will be of importance.

The energy represented by the binding together of elementary particles to form the nucleus of an atom is very great and in consequence the successful attack on the problems of nuclear structure had

to await the development of technics by means of which very high energies could be imparted to atoms or their nuclei. One of the most familiar methods of imparting kinetic energy to a large body is to allow it to fall under gravity. Unfortunately, the energy that would be gained by an atom falling freely from a great distance to the surface of the earth is too small by a factor of about a million to effect a nuclear disintegration. However, it is possible to accelerate atoms to very high velocities by means of electrical rather than gravitational forces. All atoms are normally uncharged but they are made up of a relatively massive positively charged nucleus surrounded by a sufficient number of negatively charged electrons to form a neutral aggregate. It is relatively easy to remove 1 or more of these electrons from the atomic structure, leaving a positively charged residue known as *ion*. If this ion were placed in an electric field, such as that which would be produced between 2 parallel plates connected to the terminals of a battery, it would be accelerated toward the negative plate, and if its progress were unimpeded by other atoms in its path, it would strike the plate with a high velocity, the value of which would depend on the battery voltage.

The electrical technic of accelerating ions also leads to the most convenient way of describing their ultimate energy. From the definition of electrical potential difference it is necessary to do an amount of work given by the product  $qV$  to transport a particle with a charge  $q$  between 2 points whose difference in potential is  $V$ . Conversely, if the particle falls freely through this potential difference it acquires a kinetic energy equal to  $qV$ . It is more convenient for a number of reasons to describe the energy of an atomic particle in this way than to specify its mass and velocity. One of these

reasons is that there is a natural atomic unit of electric charge which is that possessed by an electron. It is equal to  $-1.60 \times 10^{-19}$  coulombs and is generally represented by the symbol  $e$ . Atomic nuclei have positive charges equal to integral multiples of this unit. Thus, if  $n$  electrons are removed from a normal atom leaving an ion with a charge  $ne$  and this ion is permitted to fall freely through a potential difference of  $V$  volts it acquires an energy of  $neV$  joules and is said to have an energy of  $nV$  "electron-volts." For nuclear processes this unit is rather small; a neutron, for instance, is bound in an atomic nucleus with an energy of from 5 to 8 million electron volts, and hence the energy unit generally employed is a million electron volts, which is abbreviated to MeV.

The obvious direct method of obtaining high energy or high velocity ions is to maintain a large potential difference between 2 electrodes in an evacuated region and to allow ions to stream from the neighborhood of one to that of the other. When potential differences of several million volts are involved, this method is beset with difficulty. Large dimensions are involved in order to prevent electrical breakdown in the surrounding air. Suitable vacuum tubes are difficult to construct, and the maintenance of an optimum internal pressure is very critical. In spite of these and many other difficulties, the original method of development followed these lines. Pioneer work with transformer-rectifier equipment, resonance transformers, and surge generators was done by Coolidge, of the General Electric Company; Tuve, Breit and Hafstad, of the Carnegie Institution; and Brasche and Lange, in Germany. Cockcroft and Walton, in Cambridge, were the first to employ these direct methods to produce artificial nuclear disintegration. Their experi-

ments, in 1932, employing potentials of the order of 800,000 volts, represented a triumphant culmination of the program of nuclear investigation initiated by the late Lord Rutherford in 1919. This transformer technic has been further developed and extended by Lauritsen and his co-workers at the California Institute of Technology.

In 1930, a modification of the electrostatic generator was developed by Van de Graaff which is capable of producing potentials in excess of a million volts. Machines of this type operating in regions of high pressure, in order to increase the value of the ultimate potential that would produce breakdown through the surrounding gas, have been used by Wells and his co-workers at the Westinghouse Company, Tuve and his colleagues at the Carnegie Institution, and a group headed by Herb at Wisconsin, to study nuclear processes. Potentials of the order of 5 million volts can be obtained in this way and the technic presents many advantages over other methods for research in nuclear physics. Though the ultimate potentials are not so high or the ion currents so large as can be obtained with the cyclotron, the energy of the ions is more accurately controllable, more easily varied, and more sharply defined.

Several ingenious methods of obtaining high energy ions without the necessity of establishing large potential differences have been proposed but of these the only one which has so far assumed importance in the field of nuclear physics is the *cyclotron*, which was first employed for nuclear disintegration by Lawrence and his colleagues at Berkeley in 1932. This instrument is capable of accelerating larger quantities of ions to higher energies than any other device so far proposed. It has probably been the greatest technical contribution to the

study of nuclear physics and it is certainly destined to be of greater importance in the application of this field to biology and chemistry than any other type of equipment.

In the cyclotron high energies are imparted to ions by a series of successive accelerations. If ions were allowed to stream down the axis of a series of coaxial cylinders each of which was at a lower potential than the preceding one, the ions would receive successive accelerations in passing from one cylinder to the next and on emerging from the last would possess an energy equal to  $qV$ , where  $V$  was the sum of the potential differences traversed. To accelerate ions to very high energies by this method would require a very long straight path. A uniform magnetic field has the property of deflecting ions into circular paths and in the cyclotron this principle is used to confine the ions during the accelerations to a relatively limited space. The accelerating electrodes, instead of being cylinders, are in the shapes of the 2 halves of a closed shallow cylindrical box split along a diameter. An alternating potential is applied between these 2 electrodes, which from their shape are known as "*dees*," and the ions pass from the region inside one to that inside the other with the period of the alternating potential, receiving successive impulses as they cross the intervening space. They proceed outward in an increasing spiral until they achieve their maximum energy at the periphery of the *dees*.

In order to understand the operation of the instrument, this process must be considered quantitatively. If an ion of charge  $q$  is traveling with a velocity  $v$  through a magnetic field where  $B$  is the value of the induction perpendicular to  $v$ , the ion is acted upon by a force  $qvB$  perpendicular to both  $v$  and  $B$ .

This force tends to bend the path into a circle and it is balanced by the centrifugal force  $mv^2/r$ , where  $m$  is the mass of the ion and  $r$  is the radius of curvature of the circular path. Equating these 2 forces yields the relation:  $mv = qBr$ . The angular rate at which the path is described is  $v/r$ ; this is generally written as  $w$  and from the above relation we see that  $w = B q/m$ . The fact that the angular velocity,  $w$ , is independent of the linear velocity,  $v$ , is the key to the suc-

high frequency oscillator. This is essentially of the nature of a radio transmitter and produces an alternating potential difference of the order of 10 to 100,000 volts which reverses itself about 10 million times a second. During the first transit from one dee to the other, the ions gain say 100,000 electron volts; they are then bent around by the magnetic field, arriving at the space between the dees just as the electric field has reached its maximum value in the oppo-

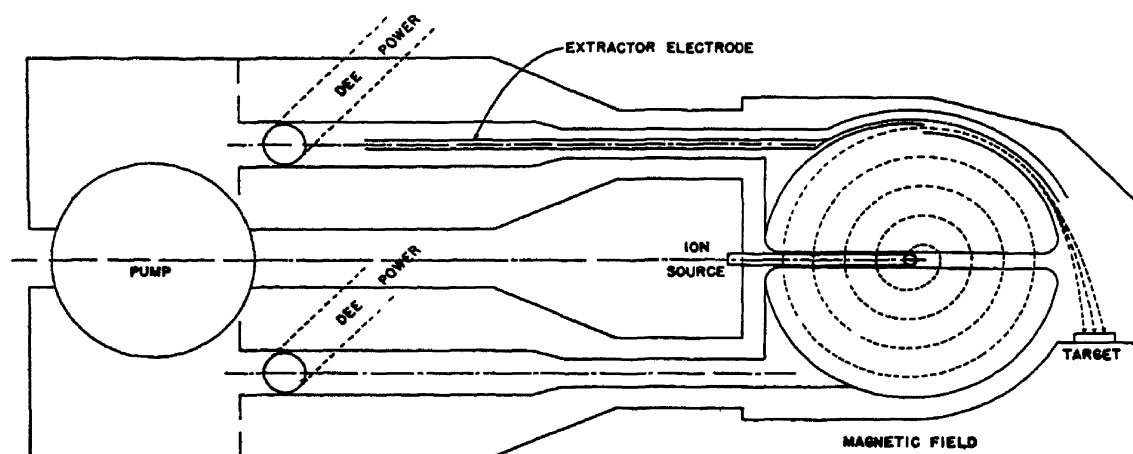


Fig. 1—Schematic section through dees and vacuum tank of 60-inch cyclotron, indicating spiral path of ions through the dees and past the extractor plate to target.

cessful operation of the cyclotron, for, from this relation it is evident that the proper resonant frequency of alternation of the potential difference between the dees is capable of accelerating all ions of the correct charge and mass from the low velocity with which they start up to the highest of which the instrument is capable.

As the instrument is constructed, these dees face one another within an evacuated cylindrical box that is placed between the poles of an electromagnet. Ions of the residual gas, which is generally hydrogen or deuterium, are produced near the center of the box between the dees by a local discharge and are drawn from this region by the electric field produced between the dees by a

site sense and are again accelerated through 100,000 volts into the dee from which they first emerged. This process continues and the ions move in circular paths of increasing radius, gaining 100,000 volts at each transit, until after making say 100 transits, which constitute 50 complete revolutions, they have acquired an energy of 10 MeV. The resonant relation between the magnetic induction  $B$  and the angular frequency of the electrical alternations,  $w$ , is generally written as a relation between  $B$  and the wave-length,  $\lambda$ , of the radio wave which would be sent out by the radio transmitter. Since  $\lambda = 2\pi c/w$ , where  $c$  is the velocity of light,  $\lambda B = 2\pi cm/q$ . From the previous relation,  $mv = qBr$ , it can be seen that the max-



imum kinetic energy that can be achieved is  $(\frac{1}{2} m v^2)_{\max} = \frac{1}{2} \frac{(qBR)^2}{m}$  where

$R$  is the maximum radius that can be described within the dees.

For convenience in dealing with hydrogen ions for which  $q$  is equal to  $e$  and  $m$  is the mass of the proton, deuterium ions for which  $q$  is again equal to  $e$  and  $m$  is twice the proton mass, or for doubly charged helium ions ( $\alpha$  particles) for which  $q$  is  $2e$  and  $m$  is 4 proton masses, the resonant condition and the energy equation may be written:

$$\lambda B = a \quad \text{and} \quad E = b R^2 / \lambda^2$$

where  $a = 394$  for deuterons and  $\alpha$  particles.  $b = 12$  for protons  
 $\quad \quad \quad = 187$  for protons  $\quad \quad \quad = 24$  for deuterons  
 $\quad \quad \quad \quad \quad \quad \quad \quad \quad = 48$  for  $\alpha$  particles.

In these equations, which may be used to calculate the performance of any cyclotron,  $\lambda$  is in meters,  $B$  is in kilogauss,  $R$  is in inches, and  $E$  is in millions of electron volts. Attainable values of  $B$  are limited, by the saturation of the iron magnet yoke, to less than 18 kilogauss, so that  $\lambda$  need not be less than 10 meters for protons or 20 meters for the heavier particles. The first of these values is inconveniently low for present radiofrequency technic, though this limitation can doubtless be overcome in the future. However, deuteron reactions will probably be of the greater importance from the medical point of view and a wavelength of 20 meters or above is entirely feasible. For this wavelength  $E = 0.06 R^2$  and hence to achieve say 35 MeV deuterons, the ions must be able to reach a radius of about 24 inches. Since the magnetic field must be uniform out to this radius an over-all pole diameter of the order of 60 inches must be used. This is the pole diameter of the large cyclotron in Berkeley. Though the amplitude of the oscillating

potential difference applied to the dees does not appear explicitly in the foregoing equations, it is essential that it be quite high, of the order of a hundredth of the output ion energy. This is necessary for 2 reasons. The number of revolutions made by the ions is half the quotient of the maximum energy by the peak potential difference between the dees. If this number is excessively large, the ions have to travel a very great distance through the residual gas in the chamber, with a consequent large probability of their suffering encounters with

the molecules of this gas and being deflected from their proper paths. Also, in large cyclotrons the energy of the ions becomes so great that there is an appreciable relativistic increase in mass which tends to destroy the resonant condition essential to the operation of the cyclotron. After say 50 or 100 revolutions, the ions would be out of synchronism with the oscillating field and would actually be decelerated, again working in toward the center of the instrument. In a large cyclotron approximately 100 kilowatts is required to maintain sufficiently high potential oscillations. The power necessary to maintain the magnetic field is also of this order of magnitude.

The first cyclotron built by Lawrence and Livingston in 1931 had pole pieces only 10 cm. in diameter. A field of 12,700 gauss was used and hydrogen molecule ions were obtained with an energy of 80,000 electron volts on maintaining oscillations between the dees with an amplitude of 2000 volts. A second instrument was constructed in 1931 with

9-inch poles with which ions of 500,000 electron volts were produced, and in 1932 the first full length paper appeared describing an 11-inch instrument that produced ions with energies in excess

MeV. Much larger numbers of ions could be accelerated with this equipment. The quantitative rate of production of high energy ions is measured by the electric current they carry to the target

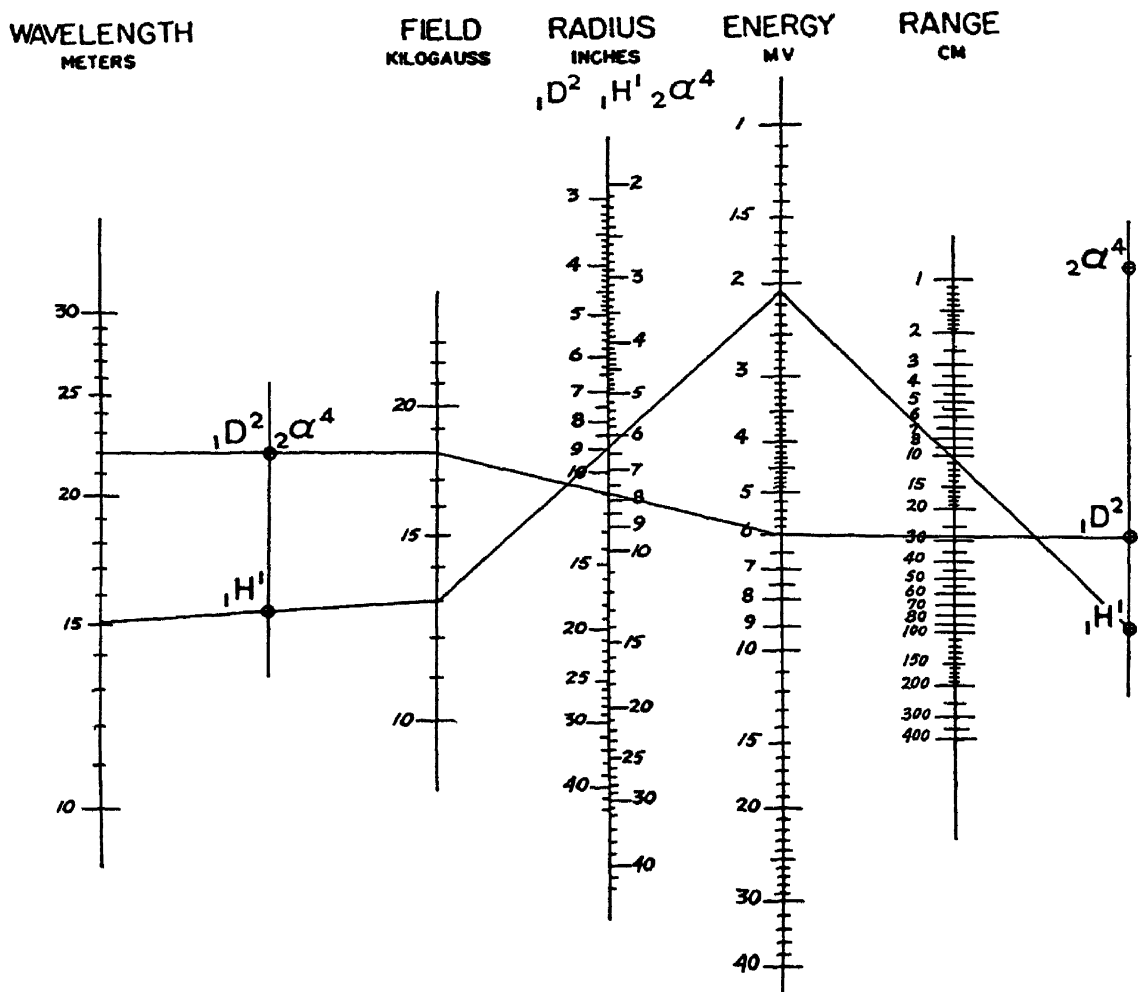


Fig. 2—Nomograph whereby energy which may be expected theoretically from any cyclotron may be calculated. A line drawn through either the deuteron-alpha particle point or through the proton point on left will cut "wavelength" and "field" lines at points which satisfy resonance condition. Another line through appropriate dee radius will give energy to be expected. Finally, a third line through appropriate index point on right will give range of such particles in air. Lines through deuteron index points shows characteristics of the 37-inch Berkeley cyclotron, while line through proton points shows same facts for the Cornell cyclotron in 1935. (Nomograph prepared by Dr. Louis Alvarez.)

of a million electron volts. The next development was to build an instrument on a much larger scale converting an old Poulsen arc magnet for the purpose. This instrument, built in 1934, had poles 27.5 inches in diameter and generated deuterons with a maximum energy of 6.3

in which they are stopped. Currents of 25 microamperes were achieved with this instrument, and, as each ion carries  $1.6 \times 10^{-19}$  coulombs, this current corresponds to  $1.5 \times 10^{14}$  ions per second. For purposes of comparison it is legitimate to recall that a gram of radium

emits  $3.7 \times 10^{10}$   $\alpha$  particles per second, each of these having approximately the energy of these deuterons. Thus, in terms of the energy emitted in the form of atomic particles, the 27.5-inch cyclotron is equivalent to about 4 kilograms of radium. The large cyclotron at present in operation in Berkeley, though one still larger is in the course of construc-

sign factors have now been fairly well worked out by the research group at Berkeley and following this design the experience on moderate-sized instruments in various parts of the country is that the cost of construction rises somewhat more rapidly than the output ion energy but as a rough figure, a minimum of \$3000.00 per MeV of deuterons must

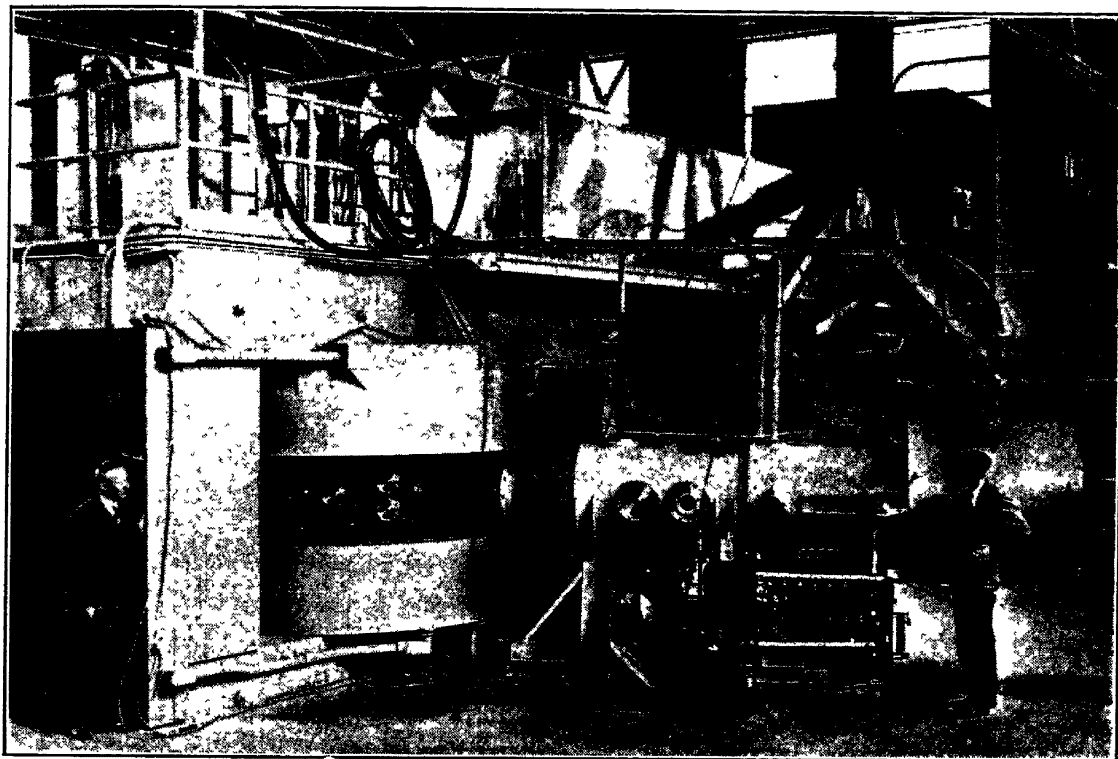


Fig. 3—Photograph of 60-inch cyclotron at Berkeley before installation of protective water tanks. Magnet and vacuum box are seen at left and dee supports and vacuum system extend to right. Concentric lines that bring radio-frequency power from oscillator are seen extending down from oscillator shield on balcony (Courtesy of Radiation Laboratory, Berkeley)

tion, has magnet poles 60 inches in diameter and when operated very conservatively produces in excess of 100 microamperes of 16 MeV deuterons, which represents a tenfold increase in the electrical power put out in the form of high energy ions.

A brief review of some of the considerations involved in the design and construction of a cyclotron is of interest in understanding its operation and the various problems that are involved. The de-

be allowed. The present consensus is that a cyclotron capable of producing 15 or 20 MeV deuterons will serve to explore all the medical possibilities now envisioned. Very important work is being done with smaller cyclotrons, but they would seem to be inadequate for undertaking properly work in neutron therapy. Once the budget or the limitations of the program have determined the maximum ion energy to be obtained, the instrument can be designed.

The *magnet* is one of the principal items to be considered. Since the saturation properties of iron limit the attainable field to about 18 kilogauss, the pole radius is determined by the type of ion and the energy. In order to apply the resonant frequency to the dees without excessive power consumption, the electrostatic capacity between these electrodes must be kept low, which requires a fairly large gap between the pole pieces for the vacuum chamber containing the dees. In practice this is of the order of one-fifth the pole diameter. In order to obtain the magnetic field across this gap a certain number of ampere-turns is required for the magnetizing coils. The square of the product of this quantity by the mean coil diameter is proportional to the product of the mass of copper in the windings by the power consumption. Thus the amount of copper to be used is determined by balancing its cost against the cost of power and the expense involved in its dissipation. When this question has been decided, the cross-section of the copper conductor to be used determines the electrical characteristics of the d.c. generator required. There is some latitude in the cooling design, the shape of the magnet yoke and its construction, tapering of the pole pieces, etc., and for these details reference should be made to the original literature. The fact that about 200 tons of steel and 40 tons of copper are employed in the 60-inch Berkeley cyclotron gives some idea of the engineering problems involved in its construction.

The *oscillator* for supplying radiofrequency power to the dees and the coupling system employed is another item of major importance. It has been mentioned earlier that a large radiofrequency voltage must be supplied to these electrodes if large currents of high energy ions are to be obtained. Assuming that

the peak radiofrequency potential is to be of the order of 1 per cent of the final deuteron energy, the circuit can be designed and the power requirements determined. The square of the radiofrequency potential is proportional to the product of the  $Q$  of the circuit (a design figure of merit) and the power dissipation, and inversely proportional to the product of the oscillation frequency and the electrostatic capacity between the dees. The last 2 factors have been determined by the magnet design, and the available radiofrequency technics determine a maximum value for  $Q$ . Thus the minimum power required is fixed and what is essentially a radio transmitter of this power capacity must be built. In general, the power required for this purpose exceeds that necessary for the magnet circuit and the 2 together constitute about 90 per cent of the total power requirements of the instrument.

The *vacuum chamber* between the magnet poles which contains the dees and in which the ions are formed and accelerated constitutes the third important item. The walls of this chamber must be built of nonmagnetic material and its top and bottom are massive steel discs. In these walls are the ports for admitting the dees, the ion source, and the target, as well as ports for testing and observation. In the most improved instruments the ions are produced by a low-voltage arc in the center of the chamber and a careful design of this arc housing greatly increases the fraction of ions subsequently accelerated by the oscillating electric field. The gas, which is generally deuterium, is admitted directly to this arc, in which the pressure is of the order of  $10^{-2}$  mm. Hg, and is then rapidly pumped away through the dee stems by a high-speed oil diffusion pump, so that a pressure of  $10^{-4}$  mm. Hg or less is maintained through-

out the greater portion of the vacuum chamber. This is necessary to prevent electrical breakdown and in order that the mean free path of the ions in the dees shall be long enough to permit a sufficient fraction of them to complete their circuits without colliding with the atoms of the residual deuterium. It is a fortunate fact that the geometry of both the

until it is in the path of the circulating ions. For other purposes, however, such as the production of a neutron beam, these high-energy ions must be deflected out of the magnetic field against a non-volatile target or through a thin metal window into a separate chamber containing the target to be bombarded. This deflection is accomplished by allowing

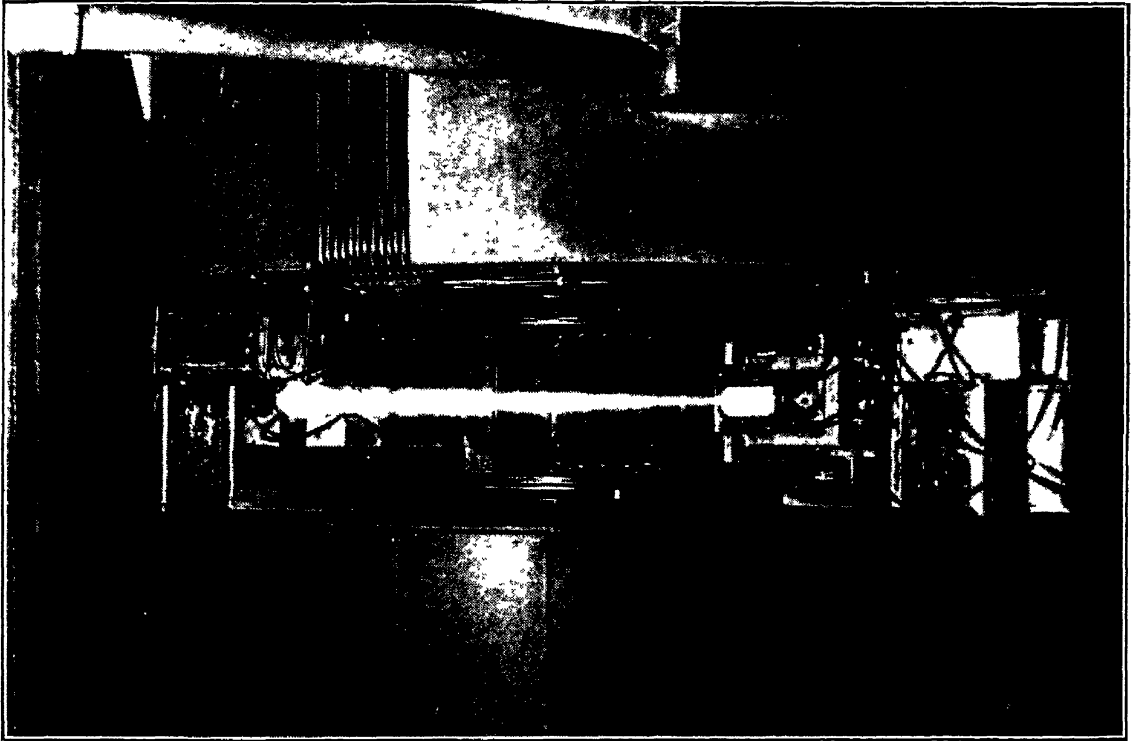


Fig 4—Photograph of a 16,000,000 electron volt deuteron beam emerging from thin window in target position (Courtesy of Radiation Laboratory, Berkeley)

electric and magnetic fields is such as to tend to retain all the ions in the median plane. If this focussing property were not present, it would not be possible to obtain appreciable ion currents at the periphery, for the initial velocity components perpendicular to this plane would result in a large vertical displacement at the end of the long spiral path of each ion.

The most efficient way in which to induce radioactivity in targets is to insert the target through a port in the chamber wall along the diameter between the dees

the ion beam to pass out of one of the dees on its last circuit of greatest radius and then applying a high electrical potential between a metal strip, known as the extractor electrode, and the dee wall in such a sense as to deflect the ion beam away from the center of the magnet and out through the weaker fringing field at the periphery. The number of ions that can be extracted in this way is only of the order of one-tenth of those actually circulating between the dees, but this technic appears to be essential for certain types of physical and biological experi-

ments as well as for neutron therapy. It is necessitated in the latter application because the beam of neutrons that is produced proceeds predominantly in the direction of the ion beam incident on the target. If the ion beam is not brought out, the distance from patient to target and the angles involved are unfavorable. The material of the target used depends on the particular purpose in mind. In order to produce a radioactive sample, a specimen of the element or that of next smaller atomic number is used as the target. In order to produce neutrons, an element such as beryllium or boron is used as the target, for the nuclear reactions brought about in these elements provide the most copious neutron sources. For a more detailed consideration of the nuclear reactions and the technics of detection, reference should be made to treatises on nuclear physics.

In the case of a medical cyclotron it is essential that all the component parts should function smoothly and consistently over periods of many hours. In order to ensure this, the design must represent good engineering practice and the materials entering into the construction must be of the best quality. A failure in the vacuum or cooling systems may not only interrupt operation but cause serious damage to the instrument. Hence, protective and interlocking devices must be used very extensively in the control system. In order that the equipment be protected as far as possible against errors in operation, as many of the controls as possible should be automatic. The construction and operation of a cyclotron requires the services of one or more physicists trained in this field as well as the strictly biological or medical staff. This personnel working with the instrument must be pro-

tected against accidental contact with electrical circuits as well as from the radiations emitted. The bombardment of the copper dees by the neutron beam makes the entire vacuum chamber a source of neutrons and gamma radiation. The target is, of course, the most intense source and the induced radioactivity after the bombardment ceases requires that great precautions be taken in manipulating targets. Several inches of lead and 3 to 6 feet of paraffin or water must be used for gamma-ray and neutron protection respectively. The controls and permanent operating personnel should be kept at as great a distance as possible to make use of the inverse square law of decreasing radiation intensity. Dosage meters should be carried by operators and blood counts made periodically. The biological effects of neutrons and a very high energy gamma-radiation are not sufficiently well known to specify accurately the precautions that should be taken and it is well to be exceedingly conservative. The work going on at the Radiation Laboratory in Berkeley and the projected programs at George Washington University and the University of Pennsylvania should lay a foundation for the proper understanding of the biological effects of these radiations.

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## NEUTRON THERAPY

By ROBERT S. STONE, M.D.

**Definition**—In recent years physicists have made rapid advances in understanding the structure of the nuclei of atoms and in discovering methods of changing such nuclei. These advances have opened up new fields of investigation and therapy for medical science. In 1932, Chadwick identified as a "neutron" a small particle of matter that came from a disrupted atomic nucleus. The neutron differs from other nuclear fragments because it has no demonstrable electric charge. Neutrons are approximately the same size as the nuclei of hydrogen atoms (protons). They do not exist free in nature but are set free by the disruption of the nuclei of some elements. They behave differently from other atomic particles because of their lack of any electric charge.

**Sources**—Prior to the development of the cyclotron by E. O. Lawrence, at the University of California, the sources of neutrons were very feeble, *i. e.*, very few neutrons were ejected per

minute. One of these weak sources was a mixture of radium and beryllium. Some of the alpha particles spontaneously ejected from the radium would strike the nuclei of the beryllium atoms and neutrons would be set free. The number of such neutrons was not sufficient to effect much change in biological material. By 1936, the cyclotron was sufficiently developed to furnish a yield of fast neutrons adequate for biological investigation, and, by 1938, for the treatment of patients with cancer.

**Cyclotron**—The Lawrence cyclotron consists essentially of a very large electromagnet, a high-frequency electric power supply, and a vacuum chamber. In the vacuum chamber ions of hydrogen (protons), of heavy hydrogen (deuterons), or of helium (alpha particles) are produced by sending a small stream of the gas over a heated filament. The ions being charged, particles are set in motion by the high frequency current and are forced to travel in circular paths

by the magnetic field. At each half revolution they are given a new charge of electrical energy as they pass across the space between the rapidly changing positive and negative fields. When the cyclotron is used to produce fast neutrons, deuterons (nuclei of heavy hydrogen) are used in the vacuum chamber. If these deuterons are given 400,000 volts of energy with each revolution they make in the vacuum chamber, and if they make 40 turns, they emerge with 16 million volts of energy. They are then directed against a beryllium target and fast neutrons are ejected in all directions.

It is necessary to stop all the neutrons except those traveling in a desired direction, in order to protect the workers in the laboratory and to protect all parts of the biological material or patients except those that are to be irradiated. Neutrons pass through heavy elements like lead quite easily but are stopped more readily by light elements such as hydrogen. Aebersold developed a "collimator" consisting of a 70 cm. wall of paraffin with a channel tapering through it from the target to an outlet or "port." Because penetrating gamma rays are also produced at the target and in the paraffin (when the neutrons are stopped), the wall had to be covered with 4 inches of lead. A filter of 3 cm. of lead was placed in the channel to stop the x-rays from reaching the port. The channel was so constructed with removable parts that fields of 3 different sizes were available: 7 x 7 cm.; 10 x 10 cm.; and 10 x 15 cm. It was found that beams of fast neutrons coming from the ports were very sharply defined.

**Measurement**—The measurement of the intensity of the beam is accomplished by using ionization instruments similar to those used for x-ray intensity measurements. These measure the amount of

energy absorbed in a given volume by measuring the ionization produced. Since it is believed that biological effects are due to the ionization produced, this method of measurement should be the most satisfactory for studying biological effects. Since, however, all of the factors involved are not fully understood, an arbitrary unit of measurement was adopted. This unit is called a "*neutron unit*" and is abbreviated as "n." It is that quantity of fast neutrons that will discharge the 100 r chamber of the Victoreen condenser r-meter to the same extent as will 1 roentgen of x-rays. It must be remembered that this is an arbitrary unit and because of certain physical factors 1 neutron unit as so measured does not represent the same amount of ionization in tissue as does 1 roentgen. From purely physical measurements it would seem that 1 n will cause about 2.5 times as much ionization in tissue as 1 r. Biological comparisons indicate a much greater effect of neutron units as compared with roentgens in the case of the human skin it is more nearly  $6\text{ n} = 1\text{ r}$ .

**Biological Tests**—Many biological test objects have been used to compare the effects of neutrons and x-rays and they show that there is no agreement between the various test objects. If the quantity of each type of radiation required to kill 50 per cent of *Drosophila* fly eggs is taken as 1, then it took 20 times that amount of x-rays to produce a given effect on mammary tumor transplants and only 8 times that amount of neutron rays. The actual values are of little significance clinically, but it is important that they are not the same. Otherwise, neutron rays would be expected to act just the same as x-rays. Should it turn out that the ratio of the skin erythema dose to the tumor-killing dose of neutrons is much less than for



x-rays, then it should be possible to cure more patients of cancer with less effect on the skin with neutrons than with x-rays.

There is a physical basis for expecting a different biological effect. The density of the ions per unit of path is over 100 times as great in the case of ionization produced as the result of neutron radiations as in that produced as the result of x-ray radiations. Zirkle has shown with alpha particles that the effect of ionization on fern spores is greater when the intensity of ionization per unit of length of the path is greater.

It is of extreme clinical importance to know whether or not the neutrons, little particles of matter, would penetrate the tissues to a sufficient depth to treat deep seated *cancer*. The physical and biological depth dose measurements are not yet very completely worked out, but Larkin working with *Drosophila* eggs and Aebersold with a Victoreen condenser r-meter have established a value of 42 per cent at 10 cm depth when a field 10 x 10 cm. in size at the surface is irradiated. This should be sufficient to obtain results inasmuch as it compares favorably with the depth dose measurements from 200 Kv. x-ray apparatus.

**Treatment**—In September, 1938, treatments were started on patients using 8 million volts. The apparatus was available only once a week, so that relatively large doses were used. Such large infrequent doses had been found to be comparatively useless with x-rays and they were found to be so with neutrons. They were used, however, to try to establish a basis from which to start more intensive treatments. Of 24 patients treated, only 9 lived more than 1 year and only 1 of these was apparently free of tumor. Only 2 were still alive on January 1st, 1941.

From this group it was found that about 90 to 100 n produced a minimum pigmentation reaction on the flexor surface of the forearm. This reaction is very similar to that produced by 650-700 r (on skin) of x-rays with 1.05 HVL in Cu. It was also found that from 200 to 270 n delivered to the skin of the side of the neck would produce a well marked erythema without blistering.

In November, 1939, the 60-inch (220 ton) medical cyclotron, operating to produce 16 million volt deuterons, became available for the treatment of patients on Mondays, Wednesdays, and Fridays. The output of fast neutrons has varied around 5 n per minute. The target skin distance is fixed at 100 cm. Fractionation of the dose has been possible. Various fractions have been and are being tried, varying from 25 to 100 n per sitting. The total doses have varied from 400 n to 1000 n. The elapsed time has also varied greatly, from 7 to 60, or more days. Some of the variations have been planned, others have resulted from unstable operation of the apparatus.

The cases to be treated have been selected with care, mostly from the outpatient department of the University of California Hospital. So far (January, 1941), they have been cases which in the judgment of the surgeons and radiologists were incurable by surgery or radiation. Thus, the chance for many survivals is not great, unless the neutrons prove very efficacious. Those patients with *cancer in the mouth and throat* have had either large ulcerated sloughing, primary lesions, or extensive neck metastases. The patients with *cancer of the breast* had metastases beyond the axilla or were treated preoperatively. The *prostatic cancers* had already spread into surrounding structures so that radical operation had been considered inadvisable.

With the large total doses the skin reactions have been carried to the extent of extensive epidermolysis. Many cases have taken from 2 weeks to 3 months to heal. The mucosal reactions in the mouth and throat have varied from mild erythema to extensive epithelitis. From the large doses there has been a great deal of subcutaneous edema and later fibrosis.

The general *reactions* of the patients have been very similar to those produced by x-rays. In some instances there was no constitutional reaction, in others there has been great prostration with nausea and vomiting.

*Microscopic sections* of materials removed during and after treatment have shown much the same changes as are seen after x-ray irradiation. It is too soon to be able to compare the changes with the varying doses.

Up to December 31st, 1940, 66 patients have been treated. The primary tumors of these patients were located as follows:

Tongue .....	11	Mucosa of mouth
Pharynx and larynx	6	(floor, roof, gums,
Lip .....	8	cheek) .....
Breast .....	7	Skin .....
Prostate .....	6	Gastrointestinal . . .

One in each of the following: Brain, bronchus, melanoma (of face), ovary,

parotid, shoulder (fibrosarcoma), Hodgkins' disease, leukemia, lymphosarcoma.

Of the patients with these conditions, 38 were treated for the first time for the primary lesion, 15 were treated for metastases, and 13 were treated for recurrences after surgery, x-ray or radium treatments.

In summary it can be said:

(1) The intensity of ionization of fast neutron beams can be measured with sufficient accuracy for clinical purposes.

(2) The beam of fast neutrons can be collimated satisfactorily for clinical purposes.

(3) Biological and physical measurements show a possible advantage of fast neutrons over x-rays.

(4) The method of administering neutron therapy is very similar to that of administering x-ray therapy.

(5) The skin, mucosal, and general reactions are somewhat similar to those produced by x-rays.

(6) Under neutron radiations, cancers have been observed to undergo regression without apparent irreversible damage to neighboring normal tissue. This applies also to metastases in lymph nodes.

(7) The results obtained to date are sufficiently satisfactory to encourage a much wider trial of this new weapon.

## BODY SECTION ROENTGENOGRAPHY

By HUGH M. WILSON, M.D.

**Definition**—Body section roentgenography describes any of several technical methods of making roentgenograms of planes or layers. It is a generic term that includes many methods which utilize a basic fundamental principle. Several workers in various parts of the world independently discovered the principle

and devised practical methods of application which have been reported under a variety of names. These include, *stratigraphy* of Vallebona, *tomography*<sup>1</sup> of Grossman, *planigraphy* of Zides des Plantes, and *laminagraphy* of Kieffer.<sup>2, 3</sup>

**Basic Principle**—The fundamental principle utilizes relative motion between

the x-ray tube, film and the object to be radiographed in such a way that the shadow of a selected plane remains stationary on the film while the shadows of all other planes have relative motion and are, therefore, blurred.

The elimination of unwanted shadows beyond a selected plane can be obtained either by rotating the body between a stationary tube and film, as described by Vallebona, or can be obtained somewhat more easily by moving the tube and film about the stationary body. The *tomograph* accomplishes this motion of the tube and film along concentric segments of arcs, meanwhile maintaining the orientation of film surface to the body. *Planigraphy* accomplishes the motion of tube and film along planes parallel to each other and to the film surface. *Laminagraphy* accomplishes the motion of tube and film in planes parallel to each other but at any angle to the film surface (usually parallel as in planigraphy).

**Details of Apparatus**—The simplest equipment now commonly employed in body section roentgenography is an attachment to the conventional horizontal Bucky table with rail mounted tube stand that will permit both the tube and film to be moved in parallel planes. Motion of tube and film is synchronized by a rigid connecting link pivoted on an arm at a point which remains stationary in relation to the body.

When the system is actuated, the tube is displaced in one direction while the film carriage is displaced in opposite direction. During an exposure the pivot point is the only plane that has no displacement relative to the film and, therefore, the corresponding plane in the body is the only one rendered as a sharp image on the film. The height of the stationary pivot point is adjustable to permit selection of various planes in the body for roentgenography.

The amplitude of tube displacement controls the thickness of the layer radiographed. If no motion is imparted to the tube, conventional roentgenography obtains and the entire thickness of the body is recorded. When tube and film are displaced through small amplitudes during the exposure, relatively thick layers are recorded; whereas, when large amplitudes of displacement occur, thin layers are recorded as the result of greater blurring of those shadows beyond the plane of the stationary pivot point of the system. This law of planigraphy may be stated as follows: *The thickness of section is inversely proportional to the angular amplitude of tube displacement.*

**Character of Blurring**—The path of travel described by the target of the x-ray tube may take any shape whatever without altering the sharpness of the image of the selected plane so long as the paths of tube and film remain parallel to each other. Linear, curvilinear or combinations of linear and curvilinear motions may be used for the tube displacement without significant alteration in the sharpness of the image. The character of the target path does affect the shape of the path traveled by shadows not included in the selected plane. Linear displacement results in an elongated blurring of these shadows, whereas circular motion of the tube results in symmetrical blurring. A round shadow not included in the stationary plane will describe an annular path on the film. Spiral motion used on the laminagraph of Kieffer,<sup>2,3</sup> and Moore<sup>4</sup> utilizes a parabolic spiral of 5 turns which results in a transverse spreading of the shadows of objects that is more efficient and produces less distortion than either linear or circular motions.

Compound motions that combine linear with curvilinear components as sine or

half sine curves have not proved advantageous over straight linear displacement in the writer's experience.

**Summary**—The general requirements for satisfactory body section roentgenography includes the following: (1) Satisfactory elimination of obscuring shadows overlying the desired plane, (2) efficient mechanical linkage between x-ray tube and film carriage, and (3) efficient absorption of secondary radiation by some form of grid or diaphragm.

It should be noted that the usual Bucky diaphragm is not adapted to circular or spiral motions. A thin wafer grid must be used for absorption of scattered radiation with these tube displacements. Longitudinal or transverse linear motions may be used with the Bucky diaphragm, but in the case of transverse motion the direction of tube displacement must occur against the direction of grid travel.

### Clinical Application of Section Roentgenography

During the relatively short period of time in which body section roentgenography has been practiced, the following fields have been explored with varying success: (1) head, (2) spine, (3) chest, and (4) appendicular skeleton. The abdomen and its viscera have received little attention by workers in body section roentgenography, since this field does not present the necessary contrasting densities that must prevail for successful application of the method. Positive contributions from application of the method are to be expected in those situations where proper contrast densities exist for successful conventional roentgenography, but in which clear visualization is difficult because of confusing overlapping structures. As a corollary to this rule, the law of diminishing returns tends to apply in studies of the appendic-

ular skeleton which can for the most part be successfully roentgenographed by right angle projections or by utilization of a decentering technic to separate overlying shadows.

**Section Roentgenography of the Head—(a) Sinuses**—The indications for supplementing conventional sinus examinations with section films are largely concerned with visualization of ethmoid and sphenoid cells that are obscured by overlying structures. The *relationship of paranasal sinus disease to ocular disorders*, as demonstrated by section roentgenography when conventional clinical roentgenographic procedures have failed to show the presence of sinus infection, has been reported by Cone, Moore, and Dean. Section examinations have been shown to clarify the extent of *bony involvement by malignant tumors of the nasopharynx and sinuses*. The technical requirements for sinus examination are usually met by 3 or 4 frontal sections at 2 cm. intervals. The frontal plane of the face must lie parallel to the film (nose-forehead position). The nares, maxillary sinuses, and anterior ethmoid cells are clearly delineated in the first 2 sections, while the posterior ethmoid and sphenoid cells usually are best defined in the 6 and 8 cm. planes. Lateral projections of the sinuses and facial bones have been found highly satisfactory for *fractures involving the paranasal sinuses* and may aid in describing the position of displaced fragments.

**(b) Temporomandibular Joint**—Satisfactory examination of the temporomandibular joint has been notoriously difficult, especially in those cases in which the joint is the site of recent trauma. Positional methods of projecting the joint region may fail to free it of overlapping shadows. The writer routinely examines this region by section

roentgenography without preliminary conventional views. Comparison films of the condyles on the 2 sides are carried out. Two exposures are made on a plane about 2 cm. above the table top, with the jaws opened and closed. Limited mobility of a condyle is illustrated in Figs. 1 and 2, which are section examinations

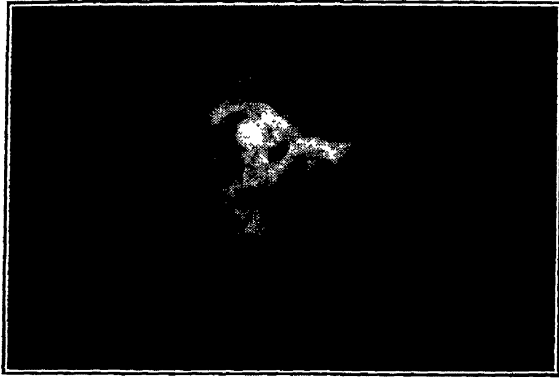


Fig. 1—Temporomandibular joint Section made with jaws in occlusion shows sharp definition of condyle and cloudiness of "joint space"

of a joint which is the site of an *infectious arthritis*. Subsequent examinations revealed destruction of cartilage and the articular bone of the condyle. *Anomalies* of the mandible as well as *fractures* are advantageously demonstrated by section roentgenography.

(c) *Mastoids*—The application of this method to the mastoids and petrous apices has been disappointing in the experience of the writer. In a few instances in which the mastoid structure was poorly pneumatized and sclerotic, a small abscess cavity or cholesteatoma has been demonstrated successfully. Comparisons of the external and internal meati on the 2 sides is facilitated by lateral section films at the proper levels. Usually the internal meatus is clearly visualized at a depth of one-third the diameter of the skull. Comparison of the 2 lateral sections may be used to supplement the information obtained from conventional

anteroposterior projections for erosion of the petrous ridges in cases of suspected acoustic neuromas.

(d) *Intracranial Lesions*—Dyke<sup>5</sup> has reported positive contributions from section studies of intracranial calcifications, particularly in those tumors in which the calcium deposits were faintly visualized on stereoscopic films. Section studies have given confirmation of the presence of suspected calcific shadows, proved their location and revealed deposits that were unsuspected from the routine films. Visibility of the intracranial fossae may be extended by section roentgenography. Frontal sections of a skull with sphenoid ridge hyperostosis may demonstrate orbital involvement previously obscured by the dense shadow of the roof. Dyke has pointed out the value of section roentgenography to those observers possessing limited or defective stereoscopic vision. Serial sections offer objective evidence of spatial relationships that surpasses stereoscopic impressions.

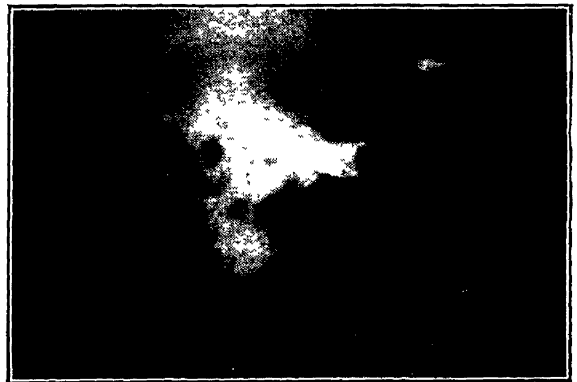


Fig. 2—Temporomandibular joint illustrated in Fig. 1. Section made with jaws open shows limitation of movement of condyle.

The contributions derived from section examinations of air studies of the *ventricles* and *subarachnoid pathways* is illustrated on Fig. 3. The posterior portion of the third ventricle, the aqueduct and fourth ventricle are structures pre-

senting peculiarly difficult and important problems to radiologists and neurosurgeons. Roentgenography of these structures by positional technics has never been entirely satisfactory, as evidenced by the numerous technical procedures that have been described for their visualization. Dense sclerotic mastoids may obscure the lateral view of the fourth ventricle. Air-filled subarachnoid sulci may obscure the iter, and dilatation of

of the atlanto-occipital joint is seldom possible from anteroposterior conventional projections and the atlanto-axial joint remains partially obscured by maxilla and occiput even with open mouth technic. Section roentgenography eliminates these structures from the desired shadows of occiput, atlas and axis. Routine section studies requires only 3 or 4 films for complete visualization of the spinous processes, laminae, pedicles and

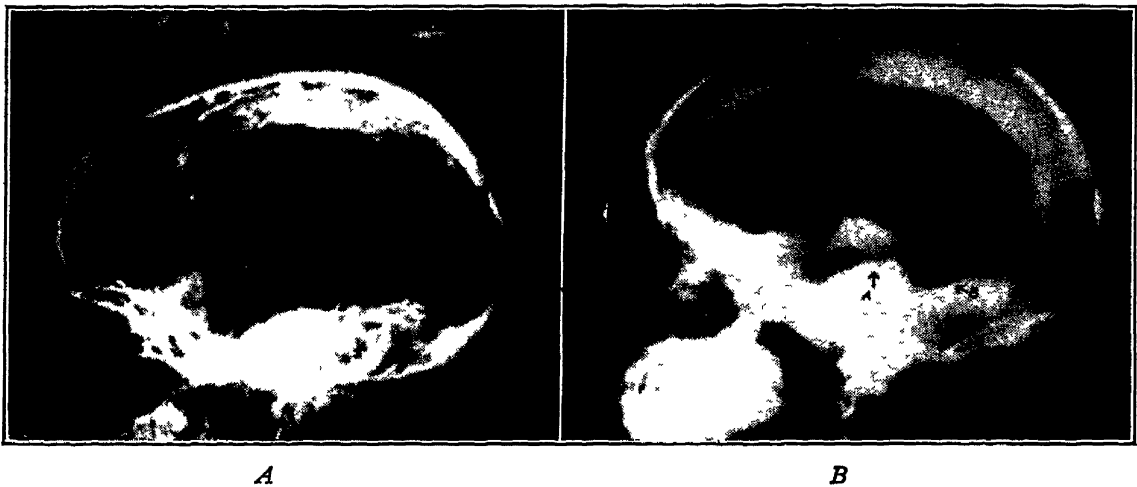


Fig. 3—Ventriculograms in obstructive hydrocephalus. *A*, Conventional lateral view with air filling posterior portions of lateral and third ventricles. *B*, Midline section demonstrates stenosis of aqueduct at arrow *A* and hernia of third ventricle at arrow *B*.

the lateral ventricles may prevent clear visualization of the posterior portion of the third ventricle. Section examinations serve to eliminate all of these obscuring shadows. Fig. 3 illustrates dilated lateral ventricles due to obstruction of the iter. The conventional film was made with occiput up, to secure complete filling of the posterior portion of the ventricular system. The posterior portion of the third ventricle and the other caudal structures are obscured. The site of obstruction could not be determined. The midline section revealed stenosis of the aqueduct (*A*) and herniation of the posterior portion of the third ventricle (*B*).

**Section Roentgenography of the Spine—Cervical Spine**—Visualization

centra. The first section is determined by the height of the external auditory canal. The odontoid process will usually lie in the same horizontal plane. By referring to a conventional lateral view, the distance of other desired structures from this plane may be determined easily. Sections at 4, 6 and 8 cm. have been found to include all of the important structures. Throughout the spinal axis, but particularly in the cervical and dorsal regions, the laminae and centra may be isolated from each other. The dorsal vertebrae in the lateral projection are more clearly visualized as a result of elimination of the overlying ribs and lung markings which tend to obscure the vertebrae. The elimination of the ribs

permits clear visualization of the spinous processes and sections made above and below the midline can be used to isolate the right and left pedicles. Conventional films of the lumbar spine are so universally satisfactory that section studies are seldom required in this region. They may be required to eliminate overlying intestinal gas shadows that simulate metastatic lesions of the spine.

rect laryngoscopy has failed to visualize the cords. The demonstration of subglottic extension of a laryngeal tumor may provide invaluable clinical data in outlining the plan for treatment.

(b) *Trachea and Bronchi*—Clear visualization of the trachea and major bronchi by conventional roentgenography requires the use of opaque contrast material for reasonable accuracy in Roent-

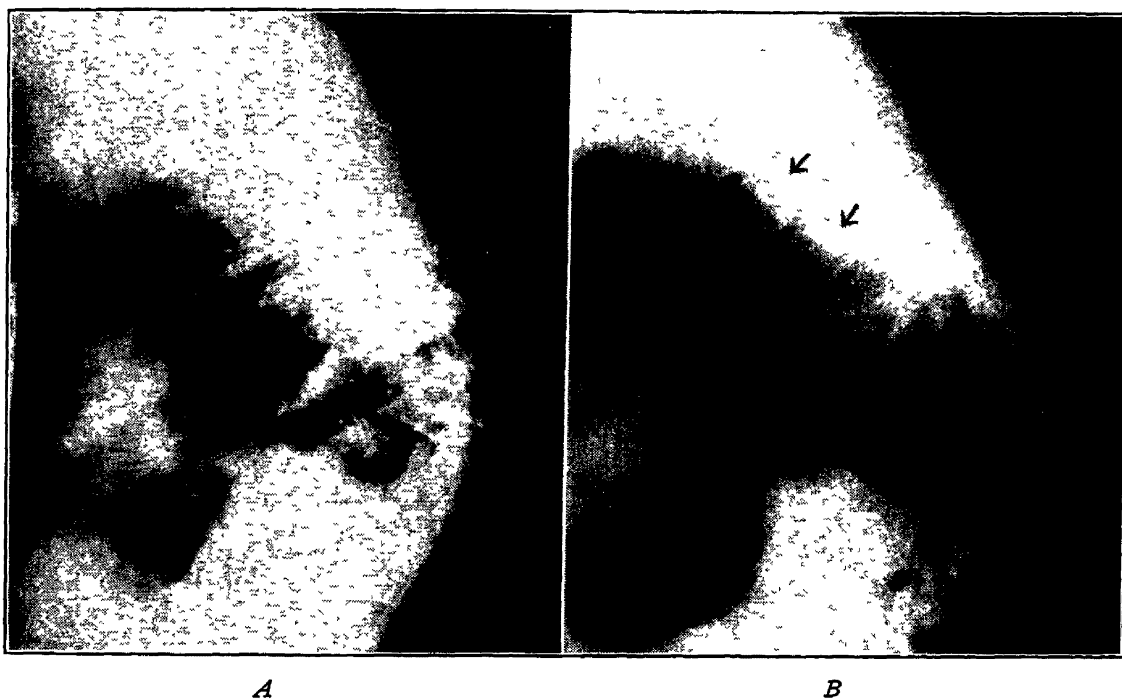


Fig 4—Tuberculosis of dorsal vertebrae *A*, Conventional lateral view (Bucky technic). *B*, Laminagram visualizes anterior involvement of vertebral bodies above kyphos.

**Section Roentgenography of Respiratory Tract<sup>6</sup> — (a) Larynx**—Roentgenographic examination of the upper respiratory tract has been extended by section roentgenographs of the larynx.<sup>7</sup> The vestibule, laryngeal folds, true cords and pyriform sinuses are clearly visualized and involvement of these structures by *neoplastic disease* may be demonstrated. Section films of the larynx at rest are supplemented by films taken in phonation to record mobility of the cords. Paralysis or fixation of a cord may be determined when indi-

gen diagnosis. Because of the limitations of conventional examinations and reluctance to submit patients to bronchoscopic examination, section roentgenography for visualization of the tracheobronchial tree must be considered a major contribution of the planigraphic methods. The importance of clear visualization of the tracheobronchial tree cannot be overestimated in view of the increasing incidence of bronchoeogenic carcinoma and the necessity for early recognition if these patients are to be brought to surgery in an operable stage. There is good evi-

senting peculiarly difficult and important problems to radiologists and neurosurgeons. Roentgenography of these structures by positional technics has never been entirely satisfactory, as evidenced by the numerous technical procedures that have been described for their visualization. Dense sclerotic mastoids may obscure the lateral view of the fourth ventricle. Air-filled subarachnoid sulci may obscure the iter, and dilatation of

of the atlanto-occipital joint is seldom possible from anteroposterior conventional projections and the atlanto-axial joint remains partially obscured by maxilla and occiput even with open mouth technic. Section roentgenography eliminates these structures from the desired shadows of occiput, atlas and axis. Routine section studies requires only 3 or 4 films for complete visualization of the spinous processes, laminae, pedicles and

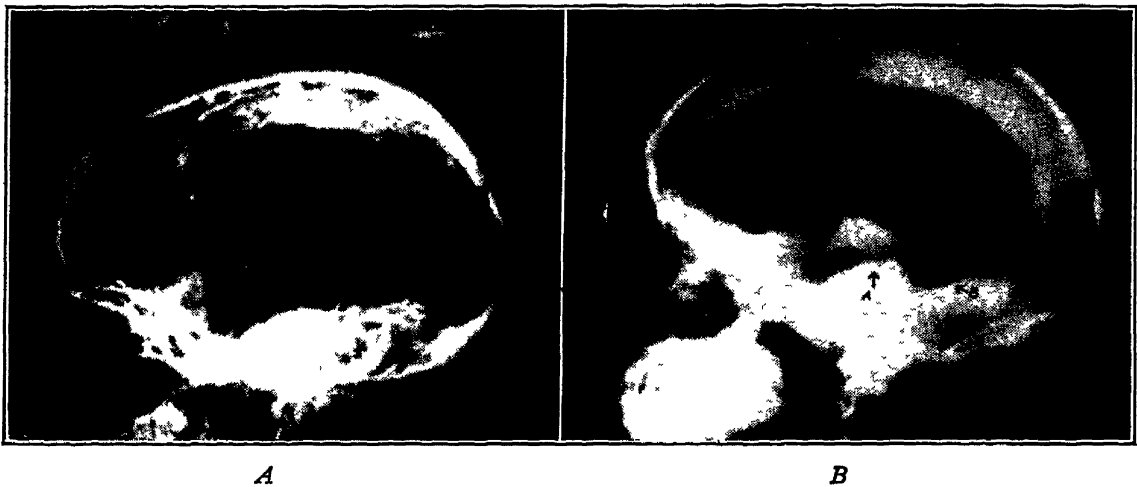


Fig. 3—Ventriculograms in obstructive hydrocephalus. *A*, Conventional lateral view with air filling posterior portions of lateral and third ventricles. *B*, Midline section demonstrates stenosis of aqueduct at arrow *A* and hernia of third ventricle at arrow *B*.

the lateral ventricles may prevent clear visualization of the posterior portion of the third ventricle. Section examinations serve to eliminate all of these obscuring shadows. Fig. 3 illustrates dilated lateral ventricles due to obstruction of the iter. The conventional film was made with occiput up, to secure complete filling of the posterior portion of the ventricular system. The posterior portion of the third ventricle and the other caudal structures are obscured. The site of obstruction could not be determined. The midline section revealed stenosis of the aqueduct (*A*) and herniation of the posterior portion of the third ventricle (*B*).

**Section Roentgenography of the Spine—Cervical Spine**—Visualization

centra. The first section is determined by the height of the external auditory canal. The odontoid process will usually lie in the same horizontal plane. By referring to a conventional lateral view, the distance of other desired structures from this plane may be determined easily. Sections at 4, 6 and 8 cm. have been found to include all of the important structures. Throughout the spinal axis, but particularly in the cervical and dorsal regions, the laminae and centra may be isolated from each other. The dorsal vertebrae in the lateral projection are more clearly visualized as a result of elimination of the overlying ribs and lung markings which tend to obscure the vertebrae. The elimination of the ribs



dence that diagnostic accuracy has improved and it is hoped that section examinations may aid materially in further advancement. The section examination supplements bronchoscopy and often points to the necessity for carrying out this procedure.

The site and character of *broncho-stenosis*, the extent of *extrabronchial tumor*, the presence of *bronchiectasis* distal to obstruction may all become obvious from serial examinations of a lung that presents only unilateral opacity on con-

scopic examination is more difficult than in the case of tumors arising in the larger bronchi.

(c) *Foreign Bodies*—Opaque and nonopaque foreign bodies of the respiratory passages may be listed as indications for section examination. Considerable embarrassment was experienced by the writer in 1 instance by advising against making a section examination of a patient who gave no history of foreign body aspiration. A section examination revealed a tooth in the right lower lobe

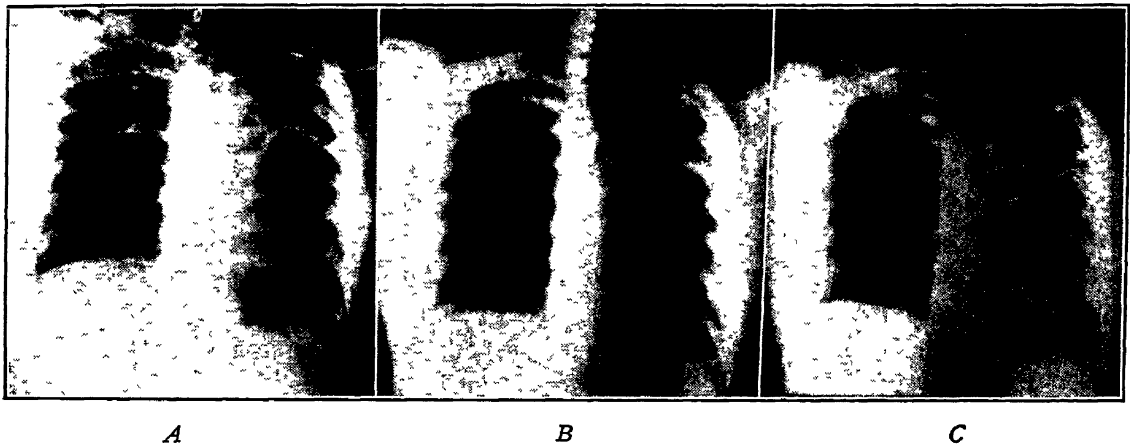


Fig. 7—Pulmonary tuberculosis. A, Anteroposterior film (Bucky technic). B, Six centimeter section shows large left apical cavity and multiple small cavities at right apex. C, Eight centimeter section shows a second large left upper lobe cavity.

ventional films. The examination of trachea and major bronchi usually requires 3 supine films for chests of average size. The relative position of the trachea may be estimated from a conventional lateral view to determine the first plane of section. A second section is made 2 cm. anterior and a third section 2 cm. posterior to the plane of the trachea. Fig. 6 illustrates a *broncheogenic tumor* which compresses both the right upper lobe bronchus and the intermediate bronchus. Primary *tumors* that arise in the periphery of the lung and infiltrate peribronchial lymphatics may be profitably examined by section roentgenography, since early recognition by endo-

bronchus. A calcific shadow visualized on conventional films was passed without recognition.

(d) *Bronchiectasis and Cystic Disease*—In the study of bronchiectasis and cystic disease of the lung the contributions are variable. Cases of bronchiectasis, in which surgical extirpation of the diseased lung is contemplated, require complete bronchograms with opaque contrast material to determine the extent of involvement. In so-called cystic bronchiectasis, however, in which pulmonary cysts are associated with bronchiectasis, it usually has been impossible to outline the extent of cystic disease by contrast material. In such cases both contrast

bronchograms and section studies may be required to demonstrate the extent of involvement.

(e) **Pulmonary Tuberculosis**—The demonstration of cavities in pulmonary tuberculosis constitutes an important field of usefulness of section technic. Proof of the presence of a suspected cavity may be found as well as visualization of entirely unsuspected cavities. Dense fibrotic and apparently healed lesions may obscure large cavities having direct bronchial communications. Sections of lungs with minimal tuberculous infiltrations have also shown cavities in planes beyond the lesion demonstrable on conventional films. Bilateral fibrotic lesions that preclude satisfactory interpretation of conventional lateral views may be sectioned in the lateral position to show the extent of cavitation in either lung. Absence of cavitation shown by section technic may contribute equally valuable data to Roentgen evaluation of the char-

acter of the tuberculous process. The results of therapeutic measures *pneumothorax* and *thoracoplasty*, are more accurately interpreted by roentgenograms that eliminate the confusing shadows resulting from these procedures.

Although serial sections may accurately demonstrate the presence of a cavity, they do not necessarily simplify the interpretation of its etiology. The differential diagnosis between tuberculous cavities and emphysematous bullae is difficult. Large bullae sometimes invaginate interlobar fissures and strongly simulate the appearance of a tuberculous cavity.

In summary, only 1 generalization regarding the *indications* for body section roentgenography can be formulated: Whenever there is reasonable doubt concerning the interpretation of routine conventional films, supplemental sections through the region may contribute valuable information.

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## ROENTGENOLOGICAL DIAGNOSIS

By PHILIP J. HODES, B.S., M.D., Sc.D. (Med.)

### Roentgen Examination of Stomach

It is now recognized that gastrointestinal disorders occasionally produce symptoms simulating cardiovascular disease. Among these conditions are *acute gastritis*, *gall-bladder disease*, *ulcers*, *carcinoma* and *diaphragmatic hernias*. The latter, though an unusual condition, is frequently attended by symptoms suggesting coronary disease. Roentgen studies of the chest and gastrointestinal system almost invariably establish the true cause of the pseudoanginal pain.<sup>8</sup>

**Roentgenological Study of Gastric Tuberculosis**—In contradistinction to the high frequency of intestinal ulceration associated with active pulmonary

tuberculosis, the occurrence in the stomach is rare. This disproportion may be attributed to the sparsity of the lymphatic supply of the gastric wall. Another factor of significance in preventing tuberculous infection in the stomach may be the physiological mobility of this organ as contrasted to the habitual stasis in the ileocecal region. Gastric tuberculosis may present numerous small miliary mucosal tubercles, numerous larger tuberculous foci, a single large tuberculous gastric ulcer or a circumscribed tumor due to a hypertrophic type of tuberculosis.

Tuberculosis of the stomach affects the pyloric end primarily and the clinical

symptoms, therefore, are those of progressing gastric obstruction. Gastric chemistry is extremely variable and the tumor mass is frequently soft in the epigastrium.

The roentgenological signs are insufficiently characteristic to be pathognomonic. The process is almost always confined to the pyloric end of the stomach and duodenum. The constricting lesion in the antrum frequently shows mucosal changes, though portions of the gastric mucosa may look normal. Fluoroscopically, peristaltic waves may be observed in the region of the lesion. The affected antrum is usually pliable and indicates that the lesion does not affect the muscular layer of the stomach. This observation is at variance with the findings in gastric carcinoma where infiltration of the walls of the stomach interferes with normal peristalsis early. The roentgenological features encountered in the antral portion of the stomach were frequently demonstrated in the duodenum. Thickening of the duodenal mucosa with single or multiple ulcerations and narrowing of the lumen of the duodenum has been observed. The mass in the epigastrium was usually smooth and somewhat tender on palpation. Under the fluoroscope it revealed a lack of fixation.<sup>9</sup>

### Roentgen Examination of Small Intestine

An increasing number of clinicians are requesting studies of the gastrointestinal tract with particular reference to the small intestines. Because of such studies the diagnosis of lesions below the ligament of Treitz is being made with increased frequency. For such studies a distilled water and barium meal is used.<sup>10</sup> In healthy individuals the head of the meal reaches the cecum in 1½ to 3 hours. The caliber of the lumen diminishes from above down. The duodenum,

jejunum and ileum can be distinguished, although the line of demarcation between them is not well defined.

There appears to be a specific mucosal pattern in the small intestines, changes in which may be due to disease and reflex changes.

A number of general conditions affect the motility of the small gut. *Nutritional edema* and *vitamin-B deficiency* produce profound disturbance in motility and small intestinal pattern. *Nontropical sprue (idiopathic steatorrhea)* is associated with striking small intestinal stasis and lacking of barium.<sup>11</sup> A number of these patients present bone changes, decalcification. Lesions outside of the abdomen will disturb the normal physiologic processes in the small intestines. These include *pituitary and brain tumors*, *nephrosis*, *diabetes insipidus*, *tabes*, *neurocirculatory* and *cardiac disease* and *spinal cord lesions*. In the abdomen, *tuberculous mesenteric nodes*, *metastatic malignancy*, *ascites*, *peritonitis*, and *gall-bladder disease* affect the tone, pattern, and motility of the small intestine.

The intrinsic lesions affecting the small gut are many. *Chronic nonspecific granuloma (terminal ileitis)* produces changes characterized by delayed motility, dilatation of the loop proximal to the lesion and the so-called "string sign." These changes are also seen in tuberculous enteritis.

*Tumors* involving the small intestine may be of any type from polyps to carcinoma, sarcoma, melanoma, leiomyoma and lymphoblastoma. Delayed motility, obstruction, intussusception, and narrowing of the lumen of the gut are among the more common findings.

*Small intestinal obstruction* due to adhesions, and any other type of obstacle is commonly associated with small gut gas. Ileus of any form, dynamic or

adynamic, is associated with intestinal gas. It is now possible, by the aid of the Miller-Abbott tube technic, to relieve such obstacles and control ileus.<sup>12</sup>

### Roentgen Examination of Genitourinary Tract

The subcutaneous injection of diodrast for renal studies in children is now a safe procedure. Normal saline (80 cc.) is used to dilute diodrast (20 cc.). The solution is injected into the subcutaneous tissue overlying each scapula, 50 cc. into each side. The films are taken at 10, 20, and 30-minute intervals following injection. No discomfort has been noticed and the wheal disappears in about 1 hour with no subsequent reaction.<sup>13</sup>

It must be remembered that urographic contrast studies may present no Roentgen evidence of a neoplasm when hematuria occurs very early in the course of its growth. Dependence, therefore, much not be placed entirely upon such studies.<sup>14</sup>

### Roentgen Examination in Gynecology

In *hysterosalpingography* the contrast substance, lipiodol, occasionally penetrates the uterine veins. Homogenous band-like streaks in the pelvic veins lasting up to 1 hour appear on the films. Spotty lung shadows due to lipiodol embolism have been seen in rare instances. Typical pulmonary infarcts have been seen following hysterosalpingography. The classical signs and symptoms of fat embolism were observed but death did not occur.<sup>15</sup>

The Roentgen diagnosis of *dermoid cysts of the ovary* has usually been based upon the presence of teeth or other calcified shadows. It has recently been observed that such calcifications are not essential for the diagnosis. A rounded or ovoid mass of decreased

density found in the pelvis should be regarded with suspicion. Usually dermoids present a well-defined ring of increased density which sharply delineates the mass from the surrounding soft tissues. The decreased density of the mass may be explained by the sebaceous material within the dermoid.<sup>16</sup>

### Roentgen Examination in Obstetrics

The Roentgen visualization of the soft tissues in *pregnancy* is a safe technic by which it may be possible to identify the position of the placenta. The diagnosis of *placenta previa* by anteroposterior or lateral films is fairly easy. Occasionally the injection of air or a dye into the bladder may be necessary. In some instances, *premature separation of the placenta* may be identified by the presence of a bulge in the uterine wall. The existence of *hydramnios* may be recognized by the disproportionately large uterus. Roentgenogram of an *extrauterine pregnancy* may be recognized by the presence of fetal parts lateral to the uterus and absence of the uterine wall over the fetus.<sup>17</sup>

Thorium dioxide may be used to demonstrate the human *placenta*,<sup>18</sup> but as it is not innocuous and it is not eliminated from the body, it should not be used. Tri-iodostearic acid is now being used experimentally, but as yet is not accepted as a regular procedure.

### Syphilis

Considerable importance has been attributed to the Roentgen diagnosis of osseous syphilis. Recent studies, however, have indicated that only a small percentage of children born of luetic mothers reveal bone changes during the first 10 days of life. In a much larger group the bone manifestations of congenital syphilis do not appear until sev-

eral months later. This reemphasizes the importance of re-examining children suspected of having *congenital lues*, several times during the first year of life.<sup>19</sup> In addition, it must be appreciated that the Roentgen bone changes once considered pathognomonic of syphilis may be closely simulated by nonluetic diseases. Among these confusing conditions are *bacteremia*, *erythroblastosis foetalis*, *hemolytic anemia*, *birth injuries*, *leukemia* and *congenital biliary conditions*.<sup>20, 21</sup>

### Cystine Urinary Calculi

The incidence of cystinuria in the population at large is probably not more than 1 in 1000. About 2.5 per cent of cystinurics develop cystine urinary calculi. The relative frequency of cystine calculi to other urinary stones is estimated at about 1 per cent. The majority of these stones are found in males and, as a rule, are usually bilateral.

Whereas pure cystine stones once were considered nonopaque to Roentgen rays, with improvement in Roentgen technic many of these stones are now seen roentgenographically. Pure cystine stones, as a rule, have a waxy appearance. They are of homogenous density and may be single or multiple. The stones are usually round and have a smooth contour. They are not as well visualized as urinary calculi containing calcium and phosphorus. There is a distinct tendency toward staghorn formation of cystine calculi. The condition is frequently bilateral.

Cystinuria is apparently hereditary in many individuals.

*Symptoms* due to cystine urinary calculi do not differ from the symptoms manifest in patients suffering with other forms of calculi. Symptoms are more usually bilateral, however, and the amount of hematuria is out of propor-

tion to the difficulty encountered with the stones. The decomposing urine gives off a vile odor of hydrogen sulfide. The finding of cystine crystals in the urine is only presumptive evidence, as chemical analysis of the stone alone will determine the degree of purity of the cystine calculus.

As cystine is known to be soluble in alkalis, the *treatment* of this condition depends upon *keeping the urine constantly alkaline*.<sup>22</sup>

### Caisson Disease

Caisson disease is due to the too rapid removal of an individual from the decompression chamber, as a result of which nitrogen is liberated as a gas from various portions of the body. Since fat dissolves much more nitrogen than other tissues of the body, lipid tissues suffer the most damage in caisson disease.

The acute symptoms of caisson disease may be referable to the spinal cord, brain, subcutaneous tissues, abdomen or limbs. The chronic lesions include pathologic changes in the bones of joints, spinal cord damage and impairment of hearing.

Roentgenographically, caisson disease of the bone is characterized by irregular areas of increased density involving the medullary portions of the bone. As a rule, ends of the long bones are primarily involved. Marked articular changes suggesting a mixed type of arthritis characterize the condition. The Roentgen appearance of caisson disease in bones is almost pathognomonic of the condition.<sup>23</sup>

### Cardiovascular Dynamics

Various methods have been developed for the study of the dynamics of the heart and vessels. One of these, the *ky-mographic method*, has been designed to automatically record the function of the

heart and great vessels by a series of outward movements. Such cardiac and vascular movements are frequently so minute and rapid that their details cannot be discerned by the naked eye.

An analysis of a Roentgen kymogram reveals the general outline of the heart and great vessels, with depressions and elevations of varying dimensions along their margins. The extreme edge of the depression indicates complete contraction of the heart, while the apex of the elevation or wave indicates complete relaxation. Close inspection of these depressions and elevations in the kymographic exposure permits one to make deductions concerning the state of the heart. It is a permanent record of a fluoroscopic observation.

As a result of *coronary artery disease*, fibrotic changes may occur in the musculature of the heart, thereby impairing the contractility of the musculature which is manifest in the Roentgen kymogram by diminished or complete absence of pulsation. In *enlargement of the heart* due to any form of cardiac disease, the entire organ or any one or more of its chambers may owe its prominence to hypertrophy or dilatation or both. In a cardiac enlargement due to hypertrophy, the pulsation of the heart border may be increased in the early stages and decreased later as a result of fibrosis or degenerative changes in the cardiac musculature. Cardiac enlargement due to dilatation is usually associated with diminished pulsation. Patients with *chronic valvular disease* present variations in pulsations in different portions of the heart, depending upon the character and location of the valvular disease. Indeed, the picture of different forms of valvular disease as registered in the kymograph is typical.

In *differentiating between mediastinal tumors and aneurisms*, great reliance is

placed upon the presence or absence of pulsation. Roentgen kymographic studies have shown that mediastinal tumors and aneurisms may show expansile pulsations and transmitted pulsations, depending upon the stage of the disease. These observations emphasize the importance of depending upon criteria other than expansile or transmitted pulsations when the differential diagnosis between aneurisms and tumor mass becomes necessary.

In an attempt to evaluate the merit of Roentgen kymography, over 500 patients were examined fluoroscopically and then by means of the Roentgen kymograph. An opinion was offered concerning the cardiovascular system following fluoroscopy which was then compared with the Roentgen kymographic study. In the vast majority of cases Roentgen kymography acted only as a confirmatory procedure. Whereas, Roentgen kymography rarely was of direct aid in diagnosis, following careful fluoroscopy it served as a valuable aid to confirm the roentgenoscopic and roentgenographic findings.<sup>24</sup>

### Roentgenographic Findings in Neurocutaneous Syndromes

The subject of neurocutaneous disease may be considered from the standpoint of the 4 outstanding clinical entities which it includes, *i. e.*, (1) tuberous sclerosis, (2) neurofibromatosis, (3) angiomas of the brain, (4) von Hippel-Lindau's disease. *Tuberous sclerosis* is a rare condition which may present the following symptoms: epilepsy, mental deficiency, acneform facial rash and congenital tumors of the eye. The pathology of tuberous sclerosis is extremely complex. The condition obtains its name from the potato-like sclerotic patches which are scattered indiscriminately over the brain. The tuberous sclerosis nod-

ules feel like a piece of hard paraffin. They show a remarkable resemblance to hypertrophic keloid formations and histologically are characterized by neuroglial proliferations. The tumors have been found in various portions of the body associated with the brain lesion. Indeed, tuberous nodules have been found in the absence of the brain lesion.

The usual history of tuberous sclerosis is that of a mild epilepsy which becomes constantly worse with age and ultimately may be directly responsible for death.

The cutaneous lesions which may be associated with tuberous sclerosis may be described as an acneform eruption usually involving the nasolabial folds. The dermatologic manifestations of tuberous sclerosis (adenoma sebaceum) are of paramount importance in establishing a diagnosis.

Occasionally subungual and periungual fibromas which looks like warts may constitute the chief complaint of the syndrome. Congenital tumors of the retina have been described.

The outstanding finding in the classical case of *neurofibromatosis* is the large number of fibromas which may cover a part or almost the entire skin surface. Pigmentary disorders in the form of spots or pigmented moles are frequently associated with neurofibromatosis. This oddity is frequently complicated by eighth-nerve tumors and other cranial nerve tumors. Nodular mediastinal tumors and large bone defects due to neurofibromas have attracted considerable attention.

An important conception in the understanding of *vascular tumors of the brain* is the finding of most malformations supratentorially and most neoformations subtentorially. Cavernous angiomatosis, with or without calcification, is found above the tentorium. Typically, angio-

blastomas are found in the cerebellum. The frequent association of vascular neval of the face with supratentorial angiomas is of diagnostic importance. These neurocutaneous syndromes produce many characteristic roentgenographic findings. Encephalograms frequently reveal the tuberous nodulations within the internal cerebrospinal pathways. Osseous defects and nodulations in the mediastinum are characteristic of neurofibromatosis. Intracranial calcification associated with the cutaneous manifestation of neurocutaneous syndromes are of considerable diagnostic importance.<sup>25</sup>

### Lipoid Pneumonitis

That aspiration of fats and oils into the lungs may give rise to a special type of pneumonitis has been known for years. It was not until recently that it was realized that lipoid disease of the lung occurs often enough to make it a relatively important pathologic and clinical entity.

Almost any oil, mineral, animal or vegetable in origin, may produce the disease. The wide use of liquid petrolatum makes it the most frequent offender.

Pathologically, the disease is characterized by its peculiar localization. It affects predominately the basal and paramediastinal portions of both lungs. Masses of phagocytes invade the alveoli and take up the collection of oil. They then enter the perialveolar tissues and obstruct lymphatics and form tumefactions like paraffinomas. Marked fibrosis ensues, bronchioles become constricted and many alveoli dilate or collapse. As the result of infection, acute, recurring or migratory bronchopneumonia may develop. Reactions to the animal oils have been the most severe.

In complicated cases, the *signs and symptoms* are meager. Cough, productive or unproductive, is common. Hemoptysis occurs often. The patients are usually afebrile. The physical signs are not pronounced or in proportion to the extent of the disease. When bronchopneumonia complicates the lipid affection, fever, dyspnea, cough, and physical signs characterize the process.

Lipoid pneumonitis plus bronchopneumonia is a grave combination of diseases and is often fatal, especially in infants. Mild or severe cases of uncomplicated pneumonitis, however, improve rapidly if further aspiration of oil is stopped.

Roentgenographically, early mild uncomplicated cases reveal fleck-like shad-

ows in the basal and central portions of both lower lobes. The right lung usually shows more involvement than the left. The flecks extend to the periphery and look like miliary mottling. With advancement of the disease, the pulmonary markings become more accentuated and nodular. In several cases discrete and confluent shadows of consolidation become evident. Later, fibrosis with dense, sharply-defined irregular or rounded shadows, varying in size and number, appear. Atelectasis, compensatory emphysema and effusion may also be evident. When bronchopneumonia develops, the roentgenologic signs become more extensive and complex, depending upon the degree of infection present.<sup>26</sup>

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## SKIN REACTIONS

By PHILIP J. HODES, B.S., M.D., Sc.D. (Med.)

Since the skin reaction has been accepted as a measure of biological effectiveness, it is important to know if similar skin reactions can be obtained by the use of kilovoltages above the 200 range as those produced by 200 Kv. radiation. In order to obtain this information, opposite sides of the same individual were treated in as nearly corresponding areas as was possible. One day the right half of the pelvis was treated with 200 Kv. and the next day the left half of the pelvis was treated with 1000 Kv. radiation. By this method the opposite sides of the same patient could be compared as to skin effect. These studies showed that similar skin reaction could be produced by 200 Kv. and 1000 Kv. radiation. The physical doses as measured by an ionization chamber necessary to produce the same skin effect was not the same. It re-

quired approximately 25 per cent more roentgens in total skin dose of the 1000 Kv. radiation.

To produce these similar reactions the fractional daily doses as well as the total doses had to be biologically equivalent and the total time elapsed also had to be the same.

The fact that patients treated with 1000 Kv. radiation required approximately 25 per cent more roentgens to produce a skin effect comparable to the skin erythema obtainable with 200 Kv. radiation does not mean that larger doses of supervoltage radiation can be given with less skin effect. What is meant is that it takes a greater number of roentgens as measured by a thimble chamber to produce the same effect. It would seem therefore, if it takes more roentgens to produce the same effect on the skin that it might take more roent-



gens to produce the same tumor effect. It would seem better, therefore, to use the term "biologically equivalent" doses

until physicists are able to accurately determine ionization of rays emitted by supervoltage machines.<sup>27</sup>

## ROENTGEN-RAY TREATMENT OF DIPHTHERIA CARRIERS

By PHILIP J. HODES, B.S., M.D., Sc.D. (Med.)

Considerable attention has been paid to the prevention of diphtheria. While immunization has played a major rôle in the public health program for the control of diphtheria, little has been done to take care of diphtheria carriers.

By definition, a diphtheria carrier is a person who harbors virulent diphtheria bacilli for a period of 21 days or more after an attack. Various methods have been suggested for controlling diphtheria carriers, among which may be included painting the throat with iodine, formaldehyde and other types of sprays. Tonsillectomy and adenoidectomy have been tried. Antitoxin has been used but seems to have no direct action on the bacilli.

Recently, *high voltage irradiation* has been employed, using rays generated at 200 Kv. filtered through 0.5 mm. Cu + 1 mm. Al. at a distance of 50 cms. Treatment was directed into both sides of the neck centering over the tonsils. Patients received 150 r to each tonsillar area at 1 sitting, 3 such treatments being given at intervals of 1 week. Cultures taken after the completion of this series of treatments were negative in the vast majority of instances.<sup>28</sup>

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# SURGERY

*Edited by V. W. MURRAY WRIGHT, M.D.*

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## ABDOMINAL SURGERY

### GENERAL CONSIDERATIONS

*By MILLARD N. LAWRENCE, M.D.*

#### **Incisions**

The principles governing incisions through the abdominal wall are simple, according to McGregor<sup>1</sup>: (1) They must give ready access to the part to be investigated; and (2) they must not weaken the abdominal wall. These principles are best obtained by observance of certain rules.

**Muscles**—In dealing with muscles, (1) whenever possible, muscles should be mobilized and displaced rather than cut; (2) if the muscles must be cut, they should be split in the direction of their fibers rather than cut across; (3) the rectus muscle deserves special consideration because of the peculiarities of its nerve supply and its investment by a fascial sheath. The nerve supply of the muscle is segmental from the lower 6 thoracic nerves; the muscle therefore may be cut transversely without impairment of its nerve supply. When the sheath is opened, the muscle may be displaced medially or laterally; it is firmly fixed to its anterior sheath by the tendinous inscriptions and, also, the outer part of the muscle is relatively fixed by the entrance of its nerve and blood supply in this region. These may be mobilized sufficiently to give access to the abdomen along the whole outer border of the muscle. Low incisions along the outer border of the muscle may divide the deep epigastric artery and nerve.

Retraction of the muscle inward must be carefully executed, since there is no question but that postoperative thrombosis frequently owes its origin to forcible retraction with damage to these blood-vessels. (4) Openings made by the incision through the different layers of the abdominal wall should as far as possible not be superimposed. (5) Materials for drainage should be inserted through separate stab incisions elsewhere, as their presence in the main wound may seriously prejudice the strength of the ultimate scar.

**Nerves**—In dealing with nerves, (1) the incision must divide no nerves. The main anatomical features concerning the nerves to the abdominal muscles are the following: (1) They are derived from the lower 6 thoracic and the first lumbar nerves. (2) They run in the direction in which the hands are put in trousers' pockets. (3) They lie between the transversus abdominis and internal oblique muscles alongside the intercostal and lumbar arteries to the abdominal wall. (4) The nerve supply to the falx inguinalis or conjoined tendon is derived from a special branch given off by the ilioinguinal nerve. This nerve is in danger in the McBurney exposure. Having given off this branch, the ilioinguinal nerve becomes purely sensory and is destined for the skin of the inner part of the groin. It emerges through the

subcutaneous ring. Here it should be secured as a routine measure and excised in all cases to be operated upon for inguinal hernia, to avoid troublesome complications which follow its inclusion in scar tissue as a result of the hernial repair. (5) The seventh, eighth, and ninth intercostal nerves enter the

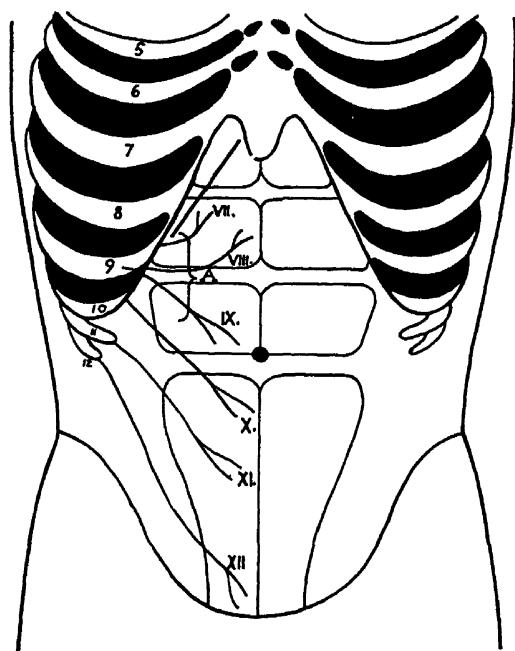


Fig. 1—Seventh, eighth, and ninth intercostal nerves entering rectus sheath from beneath ninth costal cartilage. Black bar shows Kocher's incision (drawn too short). Prolongation of lower end of incision would sever seventh nerve. Further prolongation would divide eighth and ninth nerves and paralyze half of rectus. A is the seventh, eighth, and ninth intercostal nerves bracketed together. (McGregor: Internat. Abst. Surg. in Surg., Gynec. and Obst.)

rectus sheath from under the ninth costal cartilage in the region of the gall-bladder angle. As the nerves are bunched together here and supply the upper half of the rectus muscle, their integrity should be rigidly protected. They are in danger in the subcostal incision of Kocher. (Fig. 1.)

**Anatomy of Abdominal Wall**—The anatomy of the abdominal wall is divided into 6 regions by this author. (Fig. 2.)

**Region 1**—The sacrospinalis muscle mass is a vertical column which has a segmental nerve supply.

**Region 2**—At the outer border of the sacrospinalis muscle is found a dense fascia, the aponeurosis of origin of the transversus abdominis muscle. It is formed by fusion of the layers of the lumbodorsal fascia. A vertical incision through this fascia from the twelfth rib to the iliac crest would divide no muscles but would sever the following nerves: The subcostal; the ilioinguinal, and the iliohypogastric.

**Region 3**—The area of flat muscles. The oblique, external, and internal muscles, with the transversus abdominis, form an extremely powerful muscle mass. Incisions may be made anywhere through this region provided (1) they are directed downward and inward in the direction of the external oblique, and (2) the flat muscles are split in the direction of their fibers. This is well exemplified in McBurney's incision. When a larger opening is necessary, all the muscles may be divided in the direction of the fibers of the external oblique without jeopardizing very seriously the integrity of the abdominal wall.

**Region 4**—The linea semilunaris, *i. e.*, the aponeurosis which replaces the lateral flat muscles at the outer border of the rectus. Vertical incisions through this region will paralyze the rectus muscle over a corresponding area, as the vessels and nerves to the rectus muscle cross this line.

**Region 5**—This comprises the region of the rectus sheath and the rectus muscle. As a vast majority of abdominal incisions are made in relation to this area, the region deserves special consideration. The rectus muscle is invested by a fibrous sheath which is very strong, except over the lower 4 inches of the muscle, where the posterior sheath is de-

ficient. The muscle fibers are vertical. The upper half of the muscle is divided into short segments by 3 tendinous intersections which attach the muscle firmly to its anterior sheath but not to the posterior. The intersections are troublesome in mobilization of the borders of the muscle. Their presence divides a

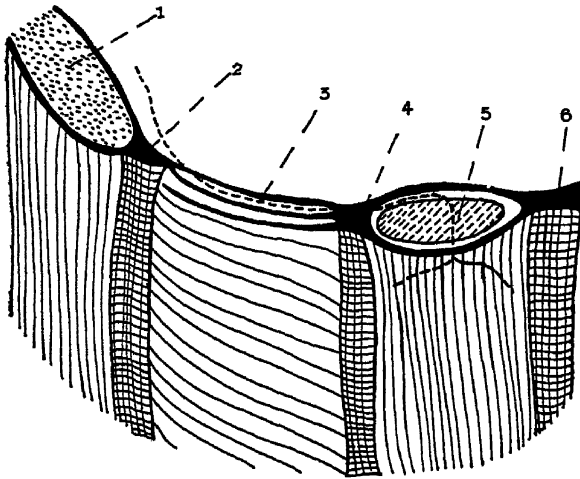


Fig 2—Diagrammatic representation of right half of abdominal parietes. Observe how 3 muscle columns alternate with 3 purely fibrous areas. Area 1, sacrospinalis; area 2, fibrous; area 3, flat muscles; area 4, aponeurosis of flat muscles (linea semilunaris); area 5, rectus in sheath; area 6, linea alba. Dotted line shows anatomy of intercostal nerves. (McGregor: Internat Abst. Surg. in Surg, Gynec. and Obst)

long muscle into several shorter segments, with resulting greater contractile efficiency. The blood supply is profuse, being derived from the superior and inferior epigastric arteries, and the lower intercostal vessels. The muscle may be safely dealt with by any of the following procedures:

1. It may be cut transversely. It is wise to stitch the muscle to its anterior sheath above and below the proposed site of section. This prevents retraction.

2. The muscle may be split in the direction of its fibers, with regard to the manner in which the nerves enter the muscle, but if the splitting is carried out for more than 1 inch, the segment of

muscle medial to the line of cleavage will be paralyzed. This is not a disadvantage when not more than  $\frac{1}{2}$  inch of muscle is medial to the cleavage.

3. The muscle may be mobilized along the whole length or any lesser extent of its inner border. Here the anterior sheath is dissected off the muscle.

4. The outer border of the muscle may similarly be mobilized in its whole length, with regard to the very special precautions to conserve the nerve supply. In displacing the muscle inward or outward, the principle of so planning the incision that after closure of the wound the intact rectus muscle intervenes between the incisions through the anterior and posterior sheaths invariably should be observed.

**Region 6**—This is the linea alba. The fibers of the rectus sheath run transversely. Vertical incisions through the linea alba weaken the abdominal wall by virtue of the fact that there is no muscle to protect the subsequent scar. Seventy-five per cent of the cases of "burst" abdomen involve midline subumbilical incisions.

#### Principles of Abdominal Incisions

—The principles which should govern abdominal incisions become very simple when it is realized that only 2 of the regions of the abdominal parietes may with propriety be attacked in gaining access to the peritoneal cavity. The purely fibrous regions should never be divided vertically. The area of the flat muscles may be penetrated preferably by the gridiron method, but, when essential, by through-and-through incisions. A vertical incision near the midline may be combined with a transverse splitting of the rectus muscle, or both recti may be divided. A transverse gridiron incision may also be combined with a vertical incision (near midline) to give increased exposure.

The realization of the principles set forth enable correct incisions to be made through any part of the abdominal wall. Some common exposures:

**Approach to Gall-Bladder**—This may be made by vertical, rectangular, or oblique incisions. The vertical incision is the usual paramedian one. This exposure presents the indubitable advantage that it may be extended to any length. The rectangular incision is merely the paramedian incision combined with transverse division of the rectus muscle. It is used when the vertical incision gives insufficient access. The oblique incision is associated with the name of Kocher. It is essentially a transection of the rectus muscle below and parallel to the costal margin. No other incision made with regard to the integrity of the abdominal wall gives such good access. It presents, moreover, the enormous advantage that only a small part of the stomach comes into the field of operation. The incision should end at the outer border of the rectus. As originally described, the incision was continued down through the linea semilunaris for 1 inch or more. If this is done, several of the nerves to the rectus muscle will certainly be divided, with resultant paralysis.

**Exploratory Incision**—This is a right paramedian incision at the level of the umbilicus. Most areas of the abdomen, excepting the most lateral, may be reached through paramedian incisions placed to one or the other side of the umbilicus. All the abdominal work of the gynecologist may be carried out through a right or left paramedian incision extending from the pubis upward for the requisite length.

**Access to Appendix**—(1) *McBurney Incision*—This is placed with its center at the junction of the lateral with the middle-third of the right spino-

umbilical line. It is made in the direction of the fibers of the external oblique muscle and is vertical to the line mentioned, which is at the midpoint of the incision. The external oblique is split in the direction of its fibers, the internal oblique and transversus abdominis muscles being sim-

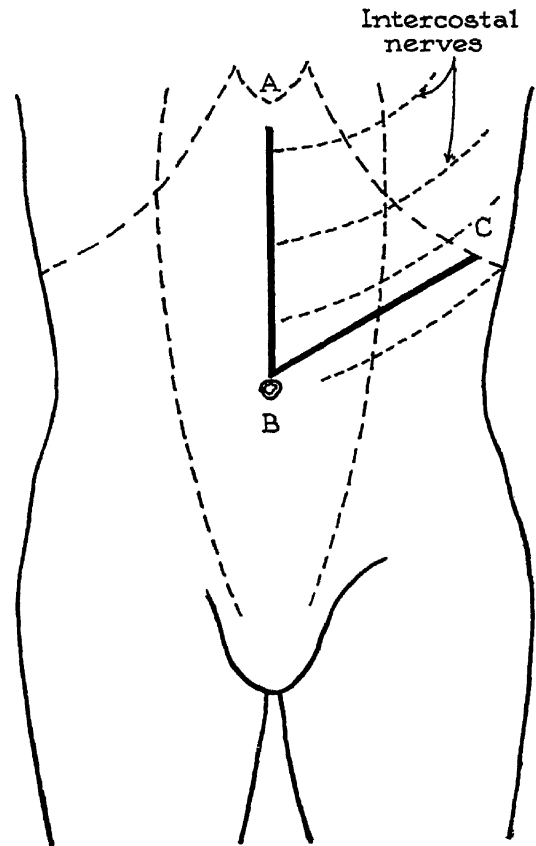


Fig. 3—How extensive access may be obtained by combining a vertical incision (AB) with an oblique incision (BC). No nerves are injured. (McGregor: Internat. Abst. Surg. in Surg., Gynec. and Obst.)

ilarly split in the direction of their fibers. Care must be taken not to damage the ilioinguinal nerve. Another disadvantage is that in enlarging the incision medialward the rectus must be retracted medially and the segmental nerves and blood-vessels may be injured.

(2) *Pararectal Incision*—This is made exactly as the McBurney but it is centered at the junction of the inner with the middle-third of the right spino-

umbilical line. The anterior rectus sheath is cut 1 inch medial to and parallel with the outer border of the muscle. The sheath is dissected laterally off the muscle, the latter retracted in, and the posterior sheath and peritoneum are divided in the same line as the anterior, great attention being paid to the nerves of the rectus. The incision is valuable in that it may be extended for any length and because the subsequent scar is sound. The incision becomes a weak one if drainage material is inserted through it into the peritoneum, as the rectus muscle is prevented from occupying its normal position and protecting the scars in the anterior and posterior layers of the sheath. Stab drainage should be used.

(3) *Paramedian Incision*—This is used when the diagnosis is in considerable doubt.

**Transverse Abdominal Incision**—This is discussed by Gurd.<sup>2</sup> The major disadvantage of this incision (Fig. 4), no matter how fashioned, is that the aponeurotic structures are cut across the direction of their strong fibers, *i. e.*, at right angles to the line of greatest strain.

The transverse incision is more anatomical, and if properly fashioned, makes it easier to expose and operate upon the abdominal viscera. Since less forceful retraction is required, less trauma is inflicted on the abdominal wall, and hemorrhage, infection, and shock are less likely to occur. The author is of the opinion that patients with transverse section of the upper abdomen have much less postoperative pain and are able to cough with little distress. They therefore can clear the bronchi of mucus and mucopurulent plugs. Gurd also considers that this type of incision produces much less postoperative hernia, painful scar, and fixation of the abdominal viscera than the vertical incision.

Whether the incision is to be above or below the umbilicus, it should never be made further away from this structure than 1 inch (2.5 cm.). If the incision be placed further away from the umbilicus, a sufficiently long incision may not be possible in consequence of the fact

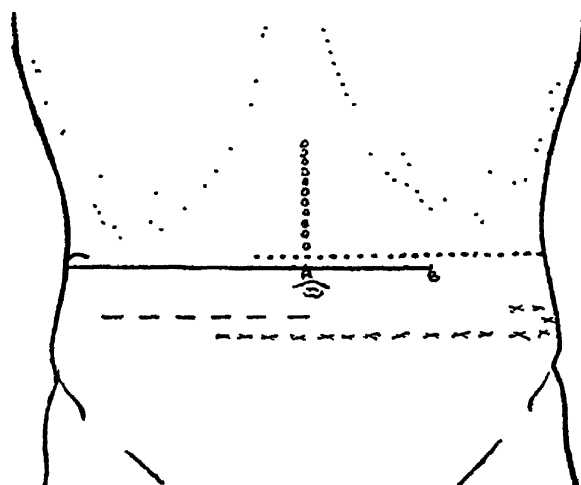


Fig 4—Diagram illustrating abdominal wall to show site of recommended incisions

———— Skin incision for cholecystectomy and exploration of bile passages. Resection of hepatic flexure *A*. For gastrotomy or gastroenterostomy *B*.

----- Skin incision for appendectomy and exploration of pelvis and terminal ileum.

..... Skin incision for splenectomy. Resection of splenic flexure.

x x x x Skin incision for resection of descending colon, abdominoperineal resection. (Similar incision on opposite side for operations within pelvis may be used.) (Gurd: Canad. M. A. J)

that either the rib border or the pelvic bone is encountered.

Although most cholecystectomies and all appendectomies can be performed easily without division of the rectus muscle, no attempt should be made to save this structure at the expense of inadequate exposure. Sound healing can be expected in all cases, except, occasionally, in the presence of cachexia or phagedenic infection.

### Disruption of Postoperative Abdominal Wounds

Donald<sup>3</sup> analyzes 27 cases of wound disruption that occurred at the Hillman

Hospital during the past 5 years and 5 seen in private practice. These disruptions were encountered in 5603 consecutive laparotomies, an incidence of 0.53 per cent. This figure probably does not represent the true incidence, as the cases are not all properly recorded. This is true especially of cases of incomplete disruption and those treated by strapping and not by secondary closure. Many hernias, not explained on the basis of gross infection, may be the result of unrecognized incomplete disruption. Upper abdominal incisions disrupted in 15, or 47 per cent, of the group; midabdominal in 6, or 19 per cent; and low abdominal, in 11 cases, or 34 per cent.

The greatest number occurred in the winter, suggesting the importance of respiratory infections and cough as an etiologic factor. Excessive intra-abdominal pressure, whether from cough, vomiting, distention or undue activity of the patient, appears to be the most important cause. Faulty or too quickly absorbable suture material, infection, hematoma, allergy and poor healing power of the tissues are thought to be secondary factors.

Close observation of the wound will make it possible to recognize disruption before it is complete and to institute proper treatment. Conservative treatment by *strapping* rather than a routine immediate secondary closure is recommended. The mortality rate in the author's series was 28 per cent; 33 per cent following secondary closure and 10 per cent following conservative treatment by strapping.

### Penetrating Wounds of the Abdomen

Storck<sup>4</sup> personally managed 46 cases, 35 of which were gunshot wounds and 11 stab wounds. He states that facilities for quick transportation, arrangements to shorten the preoperative duration of

the injuries, and provisions for promptly combating shock and hemorrhage are important in the management of penetrating wounds of the abdomen.

**Symptoms**—In penetrating wounds of the abdomen the symptoms are often indefinite. Pain is frequently slight or absent. Penetrating wounds of the abdomen which occur *via* the gluteal, sacral, or perineal regions are particularly likely to be overlooked because of the frequent absence of early symptoms.

**Physical Findings**—In penetrating wounds of the abdomen these may be misleading. Tenderness and rigidity are not constantly present. Examination of the urine for gross or microscopic blood should be made in order to reveal or confirm the presence of injuries of the urinary tract. Red blood-cell counts and hemoglobin determinations may be misleading or late indicators of hemorrhage. X-ray examination is often of value and assistance in the preoperative determination of probable injuries.

**Diagnosis**—The recognition of associated injuries, particularly those of the chest, is important in the management of this type of wound. The study of wounds of entrance and exit may indicate whether or not penetration of the abdomen has occurred. When there is uncertainty concerning penetration, exploratory celiotomy usually should be performed. Even when the wounds have been produced by small-sized shot, abdominal exploration should be done.

**Treatment**—A short interval between the time of injury and that of operation usually is favorable in its influence on the outcome, but operations should be delayed until patients have at least recovered considerably from shock. In penetrating wounds of the upper abdomen, operation may be necessary and is relatively safe during a longer period than in wounds which involve the lower

portions of the abdomen. Prolonged shock produces irreversible deleterious effects; therefore, attempts should be made to rapidly combat shock and hemorrhage. The extent of hemorrhage largely determines the outcome in penetrating wounds of the abdomen. **Transfusions** during and shortly after operation, and totaling as much as 3 quarts (3000 cc.) may be necessary. Transfusions should, whenever possible, displace saline or glucose infusions.

**Spinal anesthesia** may be employed to advantage in selected cases.

Unexpected and unpredictable visceral injuries which proved to be due to the position of the patient, or the phase of respiration at the time of injury, were frequently observed.

The total number of perforations of either hollow or solid viscera was only slightly less in the group which lived than in the group which died. Whenever perforation of 1 wall of a hollow viscus is detected, the opposite wall of the viscus should be examined for possible injury. The mortality rate was unusually low in the group of cases with injury of the large intestine, probably because of the relatively small amount of spillage which accompanies such injuries. Injuries of the gall-bladder, bile-ducts, pancreas, and kidneys are extremely serious. Perforations of the *spleen* usually require **splenectomy**. Lacerations of the *liver* causing hemorrhage may sometimes be **sutured** satisfactorily, but in other instances hemorrhage from lacerated surfaces of the liver can best be controlled by means of **packs**. Unrepaired perforations are frequently discovered at autopsy.

Because of the important relationship between hemorrhage and mortality, attention during operation should be directed first to the arrest of *bleeding*. Time-consuming procedures, such as in-

testinal resection, should be avoided whenever possible. Enterostomy is usually ineffectual, and has been displaced by better methods of preventing or combating ileus. Drains introduced into the peritoneal cavity are usually unnecessary and undesirable, but **drainage of the abdominal wall** should be instituted *when hollow viscera have been perforated*. **Silk or cotton sutures and ligatures** are superior to catgut for the repair of hollow viscera and for the closure of the abdominal wall. Irrigation of the peritoneal cavity is futile but it is desirable to suck out or pick out from the peritoneal cavity liquid blood, blood clots, detached particles of viscera, intestinal contents, and foreign bodies.

*Postoperatively*, the application of **heat** to the abdomen, the administration of large doses of **morphine**, the establishment of **gastroduodenal suction drainage**, the avoidance of enemas and flushes, and the infusion of **glucose** and **lactated Ringer's solution** are effective measures in preventing or reducing the severity of ileus and peritonitis. **Oxygen therapy** may be used to advantage in certain cases. Chemotherapeutic agents such as **sulfanilamide** and **sulfapyridine** may prove of value in reducing the mortality from peritonitis.

**Desoxycorticosterone acetate**, or other preparations containing the **adrenal cortex hormone**, may benefit those cases in which peritonitis is anticipated. **Vitamins** should be administered parenterally or orally. **Lyophilized serum** or **whole-blood transfusions** are sometimes necessary for the maintenance of plasma protein at normal level.

The *mortality* of penetrating wounds of the abdomen is disappointingly high. In the present series, the mortality in the stab-wound cases was 27.2 per cent; the mortality in the gunshot-wound cases was 40 per cent.



Ritter<sup>5</sup> considers that the 2 main causes of death in gunshot injuries of the abdomen are hemorrhage and peritonitis. He states that spinal anesthesia is contraindicated because it may produce or aggravate shock. *Ether* is most widely used and he has used *sodium pentothal* in 2 cases with satisfactory results. He further states that the necessity for speed (the operative time should not be longer than 1 hour) should not result in hasty exploration. The post-operative treatment should include the use of *antitetanic* and *gas bacillus serum*.

### Factors in Diagnosis of Abdominal Disease

**Interrelationship of Surgical Conditions of Pelvic and Abdominal Viscera**—Bainbridge<sup>6</sup> states that there are so many conditions of the pelvic cavity correlated with pathology in the upper abdomen, and *vice versa*, that any surgeon entering either cavity should be able to cope adequately as far as possible with conditions that are present in the entire area. It is often a matter of judgment, when there is much pathology present, to determine which is of primary importance and which is secondary.

The visceral anatomy of the abdomen and pelvis, when studied in a prone body, does not always give a correct picture of many conditions from which the patient suffers. The surgeon must visualize the organs in the upright position and the effect of sitting or walking during two-thirds of the daily 24 hours. In demonstrating the importance of this point the writer often has placed the patient, with the abdomen open, in the Trendelenburg position and then in the reverse Trendelenburg position. Conditions otherwise obscured or apparently absent then come into view and can be dealt with more adequately.

The author selected 18 case studies from a group of many thousands. These were presented because they had been operated upon some years ago and an adequate follow-up record was available in each instance. He is able to show by this review that abdominal and gynecological surgery are in the same family and that any limited viewpoint on the part of the ultra-specialist may cripple his surgical work, with often the same effect on the patient.

**The Kidneys**—Guardabassi<sup>7</sup> states that *Roentgen examination* of the empty abdomen may in some cases give interesting information concerning the location and form of the kidney, but examination must always be completed by *pyelography*. Either method may be used, depending on the case, but retrograde pyelography presents the advantage of giving the clearest pictures and is absolutely indicated in the presence of pararenal tumor because the other method frequently gives no picture of the pelvis and ureter in cases of this type. The author's observations in 27 personal cases confirm the fact that descending pyelography usually does not give any picture of the urinary passages on the side on which the abdominal tumor extends most; retrograde pyelography only can then give the required information of the anatomical condition of the involved organ. The 2 methods, however, must be considered as complementing each other. Two of his cases showed that the renal changes are reversible by Roentgen therapy.

There are no changes in the location and form of the urinary passages which are more or less characteristic for 1 or another tumor; aneurism of the aorta may cause the same displacements as a tumor of the lumbo-aortic lymph-nodes or an extrarenal hypernephroma. Among the author's series, there were 15 retro-

peritoneal tumors. There was more or less marked displacement of the kidney and ureter in 8 cases, while morphological or functional changes were noted in 6, and it is logical to think that displacements would have been found in some of the latter cases if retrograde pyelography had been used. Consequently, retroperitoneal tumors nearly always cause changes in the location or at least in the form of the urinary passages. On the other hand, Foerstel has claimed that there is always a pyelo-ureteral congenital dystopia in endoperitoneal tumors which are accompanied by renal displacement. This is not always true, because the Roentgen criterion to determine whether a pyelo-ureteral ectopia is congenital or not rests on the demonstrable length or shortness of the ureter. This criterion may lead to false interpretations when the following 2 basic factors are not taken into account: (1) Descending pyelography gives no result in renal compression; and (2) unless special precautions are used, retrograde pyelography does not show the exact length of the ureter, but only the length of the opaque catheter which straightens small curves and reaches the pelvis by the shortest route. The author's cases show that the renal pelvis and ureter are only rarely displaced by endoperitoneal tumors; on the other hand, these cases often present a change in the renal function revealed especially by more or less marked pyeloectasia.

**Occlusion of Abdominal Aorta—**The *syndrome* of complete occlusion of the abdominal aorta presents the classic symptoms of an acute onset with severe pain and loss of sensation in the legs, absence of arterial pulsations and rapidly progressive ascending gangrene of the lower extremities with fatal outcome. Gross and Philips<sup>8</sup> made a study of pa-

tients in whom complete obstruction of the aorta at its bifurcation was found at post mortem. The clinical picture was not at all constant. Of this study of 7 cases, 4 were patients with atherosclerosis of the coronary arteries and aorta, 2 with diffuse vascular disease involving the venous system, and 1 with chronic rheumatic cardiovalvular disease, auricular fibrillation and a ball-valve thrombus of the left auricle. The classic clinical picture occurred in only 1 of the first group of 4 cases. In another of this group there was nothing in the clinical course to suggest involvement of the aorta but at post mortem the bifurcation was completely occluded by an old gray thrombus. Of interest in the other 2 cases was the rapid progress of gangrene with speedy involvement of the opposite extremity. In the 2 cases with diffuse vascular disease, the aortic involvement seemed to be a mere incident in the course of a progressive disease involving the entire arterial tree with an arteritis in 1 and venous involvement in the other. The last case resembled in almost every detail the cases described in the literature in which complete occlusion at the bifurcation of the aorta occurred as a complication of chronic rheumatic heart disease with arrhythmia and intracardiac thrombi.

The differentiation of embolism from thrombosis as a cause of occlusion of the aorta is difficult. The authors believe that the departure from the classic clinical syndrome in 6 of their 7 cases was probably due to (1) differences in the rate of progression of the occlusion, (2) the presence of an adequate collateral circulation, and (3) subsequent development of a more efficient anastomotic circulation.

**Dystrophic Calcifications of Abdomen—**Parola<sup>9</sup> discusses the dystrophic calcifications of the abdomen en-

countered in the parenchyma of an organ or in pathological tissues.

1. **Peritoneal Calcifications**—These present such variations in localization and form that they cannot be classified; besides, they may simulate calculi belonging to various organs. They may represent remnants of tuberculous peritonitis; irregular, multiple, and mobile epiploic incrustations; meconium concretions; round eggs of parasites; particles of echinococci, calcified echinococcus cysts of regular round contour and varying size; real peritoneal calculi with opaque nuclei separated by more transparent and irregular spaces; and mesenteric cysts which are recognized by their spherical form and stratification.

2. **Calcified Lymph-nodes**—These are most frequently mesenteric or retroperitoneal; isolated; small, round, or irregular; and present an opacity similar to that of bone. They may be mesocolic, gastric, hepatic, or splenopancreatic. Lateral exposure is recommended for their recognition and they must be differentiated from renal calculi and calculi of the urinary passages.

3. **Phleboliths**—These occur in almost one-third of the adults; they are from 2 to 5 mm. thick and increase in length with the age of the patient; their density is that of bone cortex, their contour is well defined, and they usually are placed in a row. They are found in the pelvis, usually at the level of the ischiatic spine or along the upper border of the pubis; they are symmetrical and bilateral, roundish or oval, and have a more opaque center. They may be found along the ureters and must be differentiated from ureteral calculi which are located more cranial than the phleboliths.

4. **Calcification of Arteries**—This is easily recognized by its cylindrical shadow with double contour, slightly waving course, and more opaque patches

due to large calcified plaques. According to the degree of linear margins or as a homogenous streak, it may present granulations or rings. Arteriography is useful to study calcification and avoid confusion. Calcification of aneurisms of the aorta is more or less regularly annular and found in concentric layers; that of the renal arteries is rare.

5. **Calcifications of Digestive Tract**—These include enteroliths, which are found especially in the colon and the appendix and at times in diverticula of the intestinal wall: they are round, cylindrical, or oval and are formed around a nucleus of varying extraneous material. The opaque meal is useful for their recognition. Tuberculous processes and tumors of the intestine and also the wall of the stomach may be calcified.

6. **Calcification of Hepatic Parenchyma**—This is rare. Calculus of the intrahepatic biliary tract must be excluded by its lack of homogenous appearance, but the differential diagnosis is difficult and is usually made at necropsy. Phleboliths and calcified echinococcus cysts, larvae of pentastoma denticulatum or wall of the gall-bladder may be encountered.

7. **Calcifications in the Spleen**—These are still rarer. Anterior, posterior and lateral exposures are needed, with verification of the mobility of the shadow with that of the spleen; stereography, pneumoperitoneum, and splenography are useful. When the calcification is located in the hypochondrium, that of the costal cartilages must be excluded.

8. **Pancreatic Calculi**—Calcifications found in the pancreas are usually calculi; they are located on an oblique line from left to right and from above downward between the twelfth dorsal vertebra and the second lumbar vertebra.

9. **Renal Calcification**—This may be due to nephrolithiasis, tuberculosis, ab-

scess, tumors, mercury-bichloride poisoning, cysts, pseudocysts, and parasites. The possibility of retention of opaque substance must be considered and perirenal calcifications must be differentiated. Roentgen examination should be completed with pyelography.

10. **Suprarenal Calcification**—This is usually due to tuberculosis, rarely to Addison's disease. Small, semilunar opacities are found at the side of the spine above the kidney region.

11. **Calcification of Ureters**—This resembles that of the veins, but has no specific characters.

12. **Bladder Calcifications**—In the bladder, the mucosa may present calcifications in cases of tuberculosis, abscess, or toxic necrosis. Among the parasites, schistosoma hematobium is most frequently calcified and found especially at the trigonum and ureteral orifices; the wall of the bladder infiltrated by calcified eggs may give a dense, massive shadow. Calculi are differentiated from bilharziasis by their form and distinct contours. Pyelography and cystography are indicated.

13. **Urologic Calcifications**—In men, calcifications may be found in the prostate, seminal vesicles, and deferent ducts. Prostatic calculi are rare; they are usually multiple, round, and bilateral on the median line about 2 or 3 cm. above the symphysis.

14. **Gynecologic Calcifications**—In women, calcification may occur in the ovaries, the tubes, and the uterus. The only calcifications demonstrable by Roentgen examination are those of fibromyomas.

### Treatment of Abdominal Disease

In 1938, Lockwood and Ravdin<sup>10</sup> began to resort to *sulfanilamide* in the treatment of inflammatory and traumatic bowel perforations. Impressed by some

of the recoveries, they have introduced *prophylactic* use of sulfanilamide in all bowel resections. Their series consisted of 22 colon resections, 16 for carcinoma and 6 for nonmalignant disease. Ileocolostomy was employed in 6 instances. In the remainder, the involved bowel was resected and 1 or both ends of the resected intestine were brought out as a terminal or a double-barrel colostomy. In no case was there clinical evidence of peritonitis during the postoperative course.

In spite of the smallness of this series, the authors are encouraged by the prophylactic sulfanilamide therapy in the first year of its trial. In 6 instances of *inflammatory and traumatic perforation of the intestinal tract* in which sulfanilamide was used, 4 cases presented at operation a prognosis which was extremely grave. Surgeons have been hesitant about employing sulfanilamide and its derivatives in the prevention and treatment of *peritonitis of intestinal origin* because of a well entrenched belief that sulfanilamide is effective only in infections due to certain cocci. The authors gained the impression that, under special experimental or pathologic conditions which favor drug action, sulfanilamide may have some degree of antibacterial effect against almost all species of pathogenic bacteria. Peritonitis of intestinal origin is a polymicrobial infection, and the bacteria concerned in its production are relatively, but not entirely, resistant to sulfanilamide bacteriostasis. This bacteriostatic effect may become significant in the peritoneal defense against postoperative infection if an adequate concentration of the drug is present, if the number of contaminating organisms is small, if tissue necrosis is minimal and if the usual cellular defense is present. Clinical experience is as yet insufficient to warrant a final conclusion as to the

effectiveness of sulfanilamide in the prevention of peritonitis.

### Interinnomino-Abdominal Amputation

In a further review of the interinnomino-abdominal operation (hindquarter amputation) by Gordon-Taylor,<sup>11</sup> he reports 11 cases done for malignant involvement of the upper end of the femur, the innominate bone, the muscles of Scarpa's triangle and the psoas muscle. The mortality of the operation is about 1 in 3. Any great diminution in the mortality rate is hardly to be expected, despite an increased familiarity with the operation and the great improvement in preoperative and postoperative therapy.

The desirability of *nerve blocking by spinal anesthesia* and *local infiltration of individual nerves* before their division is emphasized. The insti-

tution of some form of *drip infusion*, before the start of the operation, is also recommended, since in this way the introduction of saline solution or blood can be regulated at will, to meet the requirements of the patient.

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## APPENDICITIS

By FREDERICK A. FISKE, M.D.

**Etiology**—More observations on the secretory capacity of the cecal appendage, the factors which alter its secretory capacity, and the effects of appendiceal obstruction in 235 rabbits, were reported by Dennis<sup>1</sup> and his associates. From the observations in these experiments, the authors conclude that acute appendicitis following ligation of the base of the rabbit's cecal appendage must develop in the following manner: A rise in the intraluminal pressure increases the tension on the appendiceal wall. Some of the blood-vessels are pinched off and foci of ischemic necrosis appear. These foci offer a weakened area through which rupture may occur and provide an open field for any organisms which may be present.

A review of the literature on *appendiceal oxyuriasis*, and a summary of the findings in 8 cases was made by Greene and Greene.<sup>2</sup> Opinion concerning the etiologic rôle played by the oxyuris vermicularis is divided: Some (Metchnikoff, Rheindorf, Cecil and Buckley, Riff, and others) believe that there is a definite relationship between the worm and inflammation of the appendix; others (Aschoff, Hueck, Brauch, Fisher, Drigalski and Koch, and others) doubt the ability of the worm to produce inflammation; another group (Jaroschka, Solowjew) believes that the parasite is capable of producing minute lesions in the mucosa, thereby permitting fecal matter to enter, producing inflammation. In a study of the largest series of cases

reported, Gordon was unable to demonstrate a single case in which the parasite could be definitely accused.

Mayer<sup>3</sup> reports acute appendicitis and *pinworm* infestation occurring concomitantly in several members of the same family. He feels that pinworm infestation should be considered in acute appendicitis in children, and points out that eosinophilia and perianal itching should be looked for.

An appendix containing 38 No. 6 shot discovered by x-rays during an

play a part in the etiology of appendicitis; 24 saw cases in which they believed trauma entered into the etiology. Questionnaires from 30 hospitals reporting 49,604 cases of acute appendicitis gave a history of trauma in only 11 cases. The author cannot accept the theory that trauma forces cecal contents into the appendix or forces fecaliths farther into the appendiceal lumen. If this were a fact, many more cases of acute appendicitis would be encountered following the numerous automobile ac-

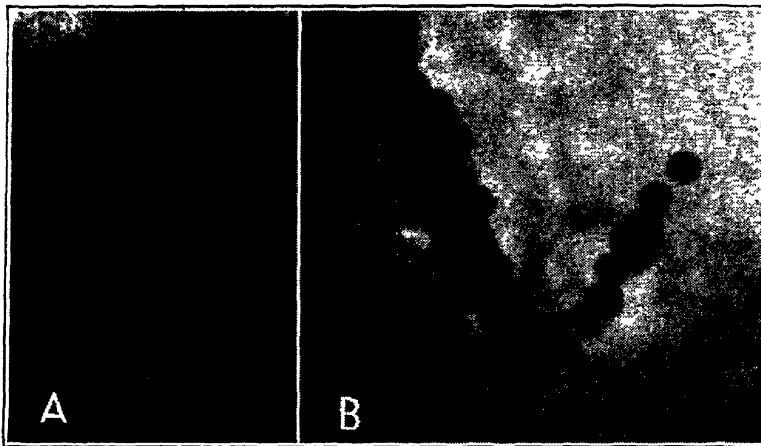


Fig. 1—Appendiceal area in *A*, spine roentgenogram, and *B*, with pressure applied under fluoroscopy. (Earl: Jour. Am. Med. Assoc.)

examination for back strain was reported by Earl<sup>4</sup> (Fig. 1). It was removed. The possibility of lead shot in the intestinal tract of game eaters must be kept in mind.

Data in response to a questionnaire on the incidence of *trauma* (external violence or muscular strain) in appendicitis in the experience of 81 surgeons operating in 72,803 cases of acute appendicitis are presented by Connell.<sup>5</sup> All these surgeons agree that trauma as an etiologic factor is rare; 31 consider that it is possible for trauma to cause appendicitis; 6 that a previously diseased appendix might be aggravated by trauma but that appendicitis cannot be initiated by an injury; and 11 that a strain can

cause appendicitis. He can conceive of an appendix being traumatized by a direct blow if it lies over the brim of the pelvis, or it could possibly be bruised if close to the anterior abdominal wall in an extremely thin individual; in such instances, however, there would be other evidence of trauma.

Bate<sup>6</sup> believes that trauma infrequently is a factor in acute appendiceal obstruction, because it is rare among the people living under peasant conditions in Europe and the tribal conditions of India, who eat meat plus an unrefined diet, and who are subject to trauma in all its forms.

**Pathology**—The pathological anatomy of acute appendicitis, which in-

cludes 2 distinct intestinal diseases, *i. e.*, inflammation of the wall and occlusion of the lumen, is discussed by Goyena.<sup>7</sup> He distinguishes 3 different anatomical forms. Catarrhal or congestive appendicitis is the initial form of any variety of the disorder and corresponds to slight attacks, the repetition of which is erroneously called chronic appendicitis by many physicians. There is slight swelling of the organ and dilatation of the subserous capillaries without exudation on the peritoneal surface. The process is limited to the mucosa. Appendicitis is present when histological examination reveals inflammatory infiltration of the submucosa and subserosa. Suppurative appendicitis begins at the bottom of 1 of the crypts from which the abscess spreads, especially in the loose tissue of the submucosa.

The epithelial covering is destroyed only at the points of evacuation of the small abscesses, but these points may fuse together to form an ulcer. Gangrenous appendicitis is due to interruption of the circulation; it may be localized and is then usually caused by compression of the inflamed wall by a coprolith, or it may be generalized and is then caused by embolism or thrombosis of the appendiceal circulation or by acute obstruction of the appendix; death from peritonitis is the rule within from 48 hours to 6 days. If perforation occurs in suppurative appendicitis, the focus is usually already isolated from the peritoneal cavity by epiploic adhesions, and a periappendiceal abscess forms; if perforation occurs in acute obstruction, the evolution is rapidly fatal. Clinically, appendicitis may start suddenly during perfect health (obstruction) or gradually after prodromal disturbances lasting several days (catarrhal or suppurative forms); in this case it may regress spontaneously; however, all 3 forms may

end in perforation and death by acute peritonitis.

**Mucocele**—Latimer<sup>8</sup> reviews the literature on this unusual lesion of the appendix, of which about 400 cases have been described. He adds 2 cases, 1 showing partial invagination into the cecum (Fig. 2), the other acute inflammation superimposed upon a mucocele. Rupture of a mucocele may lead to pseudomyxoma peritonei.

A case of appendicitis associated with complete situs inversus viscerum was reported by Lawrence.<sup>9</sup> Over 270 cases have been recorded. It is of surgical interest, because many of the patients have pain in the right abdomen although the appendix may be located on the left side. This case showed rigidity in both right and left iliac fossae, but the pain was mostly in the right, except on deep pressure, when it was more intense on the left.

**Symptoms**—Ehlert<sup>10</sup> classifies urologic manifestations of appendicitis as follows: (1) Disorders of micturition (frequency of urination, pain on urination, dysuria, and retention of urine); (2) abnormalities of the urine (hematuria, pyuria, albuminuria and anuria); (3) pain in the right testis or retraction of the testis; (4) renal or ureteral colic; and (5) tenderness in the right costovertebral angle. The operative and post-mortem observations in these cases with urologic symptoms support the theory of intimate contact of the appendix or the inflamed peritoneum with some part of the urinary tract. The most frequent site is the right ureteral wall at the brim of the bony pelvis.

**Complications**—Vale<sup>11</sup> feels that *abscess in the rectovesical pouch* is a complication which has not been adequately emphasized. In 3 years he has seen 26 cases; 21 of these occurred in 785 cases of appendicitis, a frequency of

2.67 per cent. The clinical picture of concealed abscess appearing on the fourth to seventh day, associated with fullness in the rectum, frequency of stool, and a mucoid rectal discharge are very suggestive. If the abscess is in contact with the bladder, urinary symptoms may be present. Usually some degree of small bowel distention is present, and at times

Conservative treatment by *hot irrigation* and *diathermy* are not disputed, but considerable difference of opinion develops concerning the method of approach for surgical *drainage*. The author discusses the objections to transrectal drainage which are as follows: (1) Danger of contamination from rectum to peritoneal cavity; rebuttal, it

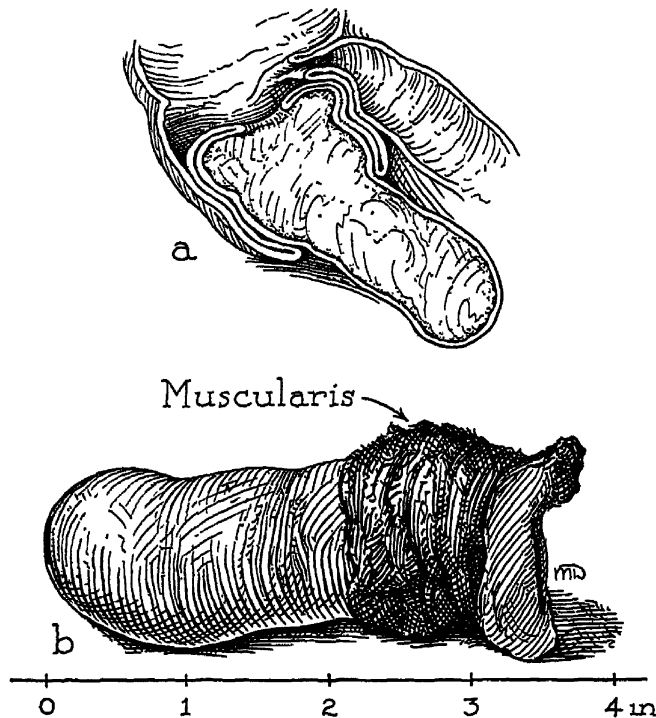


Fig. 2—Drawing of specimen of Case 1. Insert shows invagination of base of appendix into cecum. (Latimer · Am. J. Surg.)

even a complete intestinal obstruction. The author emphasizes the necessity of looking for a pelvic abscess when obstructive symptoms appear postoperatively. Relaxation of the rectal sphincter can be ascertained in 50 per cent of the cases. A palpable mass bulging into the anterior rectal wall, which may be cystic, fluctuant, or indurated with pitting edema, is located just above the prostate. At times the abscess at first may be palpated best suprapubically. It is well to examine the mass after catheterization of the bladder has been performed.

enters abscess cavity rather than free peritoneum, and in reality is a form of extraperitoneal drainage; (2) it is a blind procedure; (3) fecal fistula may be produced; if they do, spontaneous closure would occur in the absence of obstruction; (4) herniation of the small bowel, due to improper technic; (5) severe hemorrhage, which may be avoided by anterior approach with blunt scissors near the midline; (6) danger of entering the bladder, which may be avoided by catheterization; (7) continual infection from inside of the rectum; experience shows the difficulty



of keeping the tract open. Transrectal drainage was employed in 26 cases by the author, who strongly advocates this approach, without a death.

According to Neiman,<sup>12</sup> acute appendicitis complicated by *diabetes mellitus* is a serious problem, since the 2 conditions have a bad influence on each other. Early removal of an inflamed appendix is more urgent than in a normal person for 2 reasons: (1) Infection quickly aggravates the diabetes; (2) infection does not localize well. The possibility of acute abdominal symptoms (diffuse abdominal pain, abdominal tenderness, and vomiting) as a result of acidosis makes the diagnosis difficult. The following practical points are mentioned: (1) Remove the appendix first; treat the diabetes later. (2) It is not necessary to wait until the urine is sugar-free. (3) Blood sugar and CO<sub>2</sub> determinations are not imperative in an emergency, provided the urine is examined for sugar, acetone, and diacetic acid. *Insulin* is given accordingly. (4) The diacetic acid test is a reliable and satisfactory index of acidosis in surgical emergencies. If negative, operation need not be delayed. If positive, give 40 to 60 units of *insulin and saline*, repeat the test in 3 or 4 hours. *Operate* as soon as the patient is out of acidosis. (5) Diabetic consultant.

A fatal case of *gas bacillus infection of the abdominal wall* following appendectomy was reported by Breslin.<sup>13</sup> The cecal wall was perforated at operation. Death occurred in 50 hours. Necropsy revealed an acute generalized peritonitis and extensive gas bacillus infection of the abdominal wall. Apparently, the source of infection was the appendiceal stump, which was surrounded by a pericecal abscess. It was noted that the infection of the right rectus muscle was limited by one of the

tendinous inscriptions, and that the left rectus was also involved.

A case of *delayed secondary hemorrhage* following appendectomy was reported by Parker.<sup>14</sup> The patient, a male, aged 22, had a chronic appendix removed, was discharged in 10 days, and 19 days later passed much bright red blood on defecation. The bleeding continued for 12 days, when operation showed active inflammation of the appendiceal stump and the cecum. A medium sized artery was found spurting in an abscess cavity in the cecum. Cure followed. The possibility of this complication is more marked in the cases where the stump has been inverted.

**Diagnosis** — Guy and Rotondi<sup>15</sup> studied the histories of 52 patients having ovarian lesions which were erroneously diagnosed as appendicitis. These cases occurred over a 6-year period. The relation of the time of onset of the symptoms to the menstrual cycle was found to be of major diagnostic importance: Rupture of the follicle cysts occurs in the midmenstrual cycle from the eleventh to fifteenth day, while rupture of a corpus luteum cyst is more probable 7 to 10 days before onset of menstrual period. Another important diagnostic sign is sudden pain in the lower abdomen at the onset; it was noted in one-half the cases.

The history of previous similar attacks may be helpful. Vaginal or rectal examination may aid in the diagnosis. In most patients the symptoms are mild, can be correctly diagnosed, and spontaneous recovery can be expected. In other patients the symptoms are more pronounced and may so closely simulate appendicitis, tubal pregnancy, or other pelvic lesions that surgical exploration is advisable.

The *differential diagnosis* between appendicitis with peritonitis and primary

*pneumococcic peritonitis* is difficult. Jonas<sup>16</sup> found a mortality rate of 72.1 per cent for the cases of pneumococcic peritonitis operated early, as compared with a mortality of 29.2 per cent where operation was delayed. The following table gives the distinguishing features of the diseases:

ACUTE APPENDICITIS	PNEUMOCOCCIC PERITONITIS		
1. Most of the time the symptoms are minimal at first and progress gradually.	1. The onset is generally acute so that often even the exact minute is known. The symptoms are usually severe from the beginning.	8. Pain on the right side is common. The thighs are often flexed.	8. There is no typical position. The child generally throws himself about restlessly.
2. The abdominal pains are in the foreground and are localized in the umbilical region or in the right lower quadrant.	2. As in acute appendicitis.	9. Pressure pains are strongest in the abdomen.	9. Tenderness of the entire abdomen is present but is not marked.
3. There is early and repeated vomiting.	3. As in acute appendicitis.	10. There is more or less aggravation of the pain on sitting up. In peritonitis due to perforation the child refuses to sit up and tries to lie still.	10. The child sits up without resistance and does not complain of pain.
4. Herpes febrilis is not frequent.	4. Herpes febrilis is relatively common.	11. There is pain on flexing the right thigh when the appendix is near the psoas.	11. There is little if any pain on flexion of the thighs.
5. The fever does not often exceed 101.4° F. (38.5° C.).	5. The fever is high in the beginning, seldom under 102° F. (39° C.) and generally over 104° F. (40° C.).	12. Constipation is usual.	12. Diarrhea is frequent, often at the beginning.
6. The pulse is not usually more than from 120 to 130, and in the beginning is not small.	6. The pulse is generally between 140 and 160; it is small and sometimes barely perceptible.	13. Usually very little change in the facies occurs except in the advanced cases, where the hipocratic facies may be noted. The child does not appear to be very sick.	13. The individual looks very ill. There is cyanosis of the lips and the eyes are grayish.
7. There is reflex abdominal spasm and in severe cases a board-like abdomen is found.	7. Reflex spasm of the abdomen is not very marked; usually a "doughy" consistency may be noted.	14. The sensorium is intact.	14. Very often there is slight mental confusion, and, in the severe cases, coma.
		15. A discharge is seldom seen.	15. About 50 per cent of the cases have a vaginal discharge in which the gram-positive diplococcus is found.
		16. The leukocyte count is generally not over 20,000.	16. The leukocyte count ranges from 25,000 to 30,000 and is frequently found to be above this level.

Diagnostic puncture is of value in the first 48 hours before adhesions have formed [*sulfapyridine* and *sulfathiazole* probably would have reduced the mortality in these cases].

A case of perforated appendicitis and *pneumococcic peritonitis* treated by operation and *sulfapyridine* was reported by Maughan.<sup>17</sup> The case is of interest because (1) the appendix may have been the primary focus of the pneumococcal peritonitis; (2) the importance of laparotomy in suspected cases is shown; (3) the value of *sulfapyridine* in control of the pneumococcus is illustrated.

*Torsion of the appendices epiploicae* often simulates and is erroneously diagnosed appendicitis until the true pathological lesion is found at operation. Mabrey<sup>18</sup> added 6 cases to those reported in the literature, bringing the total to 52.

**Statistics**—In a survey of 8727 cases of acute appendicitis operated on at the Jewish Hospital in Brooklyn during the 20 years prior to 1935, Morse and Rader<sup>19</sup> report a mortality rate of 2.15 per cent.

That the number of deaths from appendicitis varies directly with the severity of the pathological process and the extent of peritoneal involvement is confirmed by the mortality rates of 0.5 per cent for 6464 cases of acute nonperforated appendicitis; 1.56 per cent for 1024 cases of perforation without gross peritoneal involvement; 6.03 per cent for 663 cases with abscess formation; 6.54 per cent for 336 cases with local peritonitis; and 32.5 per cent for 240 cases with diffuse peritonitis. These statistics emphasize the importance of early operation in all cases of acute appendicitis.

According to Davis and McLaughlin,<sup>20</sup> the commonest causes of

# ANNUAL MORTALITY RATE, JEWISH HOSPITAL SERIES

Period 1915-1934, Inclusive  
(Morse and Rader<sup>19</sup>)

Year	Cases	Deaths	Mortality Percentage
1915	397	12	3.02
1916	442	19	4.29
1917	404	13	3.21
1918	405	9	2.22
1919	417	12	2.87
1920	394	9	2.28
1921	393	13	3.30
1922	400	9	2.25
1923	448	11	2.45
1924	433	6	1.37
Average 2.73%			
1925	398	4	1.00
1926	405	5	1.23
1927	469	13	2.77
1928	346	6	1.73
1929	413	9	2.99
1930	468	14	2.17
1931	556	0	0.00
1932	471	2	0.42
1933	563	11	1.95
1934	505	11	2.17
Average 1.63%			
Totals	8727	188	2.15

death in acute appendicitis are purgation and procrastination. From a statistical study of 179 cases of peritonitis, secondary to acute appendicitis, it was concluded (1) that patients with a nonperforated appendicitis, usually seen in the first 1 or 2 days of the attack, should have immediate appendectomy; (2) the patient with local spreading peritonitis usually seen on the second day, or occasionally on the first or third day, should have immediate appendectomy with drainage; and (3) in patients with diffuse peritonitis most commonly seen from the third to fifth day, it was found that in those treated by immediate operation, mortality was 60 per cent, while in those in which operation was delayed it was only 14 per cent.

Observations on 635 cases of acute appendicitis were made by Busch and Spivack.<sup>21</sup> The total mortality was 15 per cent. The duration of the disease,

the use of cathartics, and diabetes mellitus were important factors in the mortality. As in other series, gangrenous perforated cases had the highest mortality rate.

A series of 1317 cases of acute appendicitis subjected to immediate operation at Johns Hopkins Hospital was reviewed by Stafford and Sprong.<sup>22</sup> There were no deaths in 838 cases in which perforation had not occurred. In 479 cases of perforation with either abscess or peritonitis there were 48 deaths, a mortality rate of 10 per cent. From a study of the fatal cases the writers consider that this could be reduced by more careful diagnosis and better treatment of postoperative complications. This mortality rate was lower than the average reported by exponents of the delayed or expectant treatment of perforative appendicitis, and they feel justified, therefore, in continuing to perform immediate operation in the treatment of appendicitis.

In an analysis of 206 patients with acute appendicitis treated from 1913 to 1925 and another group of 561 from 1925 to 1939, Ward<sup>23</sup> found a reduction in mortality from 5.8 to 3 per cent. He attributes this reduction to the use of continuous gastrointestinal decompression. In the cases in which perforation with local peritonitis occurred there was a reduction in mortality from 14.3 per cent to 5 per cent. In perforation with diffuse peritonitis, a reduction from 40 per cent to 27.2 per cent was recorded. Decompression was used preoperatively for cases with diffuse peritonitis, while in the postoperative period it is used without awaiting distention.

**Treatment**—The question of when to operate for acute appendicitis is answered by a single word: *immediately*. Mortality statistics from all sources ranging from 0 to 0.8 per cent

will prove the statement. For appendicitis complicated by peritonitis, local or diffuse, or with abscess, however, the questions of when to operate, what operation is best, or should operation be performed are still unsettled. Only individual experience can be followed coupled with a constant survey of the experience of all, in an attempt to reduce the mortality in these complicated cases.

**Immediate Operation**—In a critical review of 1039 cases of acute appendicitis, of which 860 were confined to the appendix, Barrow and Ochsner<sup>24</sup> report a mortality of 0.8 per cent. The remaining 179 cases with appendiceal peritonitis showed a mortality of 27.3 per cent. Analysis of these, according to duration of symptoms, show (1) 24 hours, 15 appendectomy with 3 deaths; 3 conservative treatment, 2 deaths; (2) 24 to 72 hours, 61 immediate appendectomy with 15 deaths; 31 conservative treatment with 5 deaths; (3) more than 3 days, 21 immediate appendectomy with 10 deaths; 31 conservative treatment with 5 deaths. Despite these statistics, the writers consider that exploratory laparotomy is a wiser procedure than conservative measures in cases in which the diagnosis of acute appendicitis cannot be established with reasonable certainty; where there is doubt about perforation; and when the case is seen within the first 24 hours. If exploration reveals a well walled-off process, no attempt should be made to disturb it; however, if free fecal contamination from the perforation is found, the best chances are offered by removal.

In the conservative treatment emphasis must be placed upon careful clinical search for (1) infections of the *cul-de-sac*; most common; detected by digital examination every other day; treated by rectal or vaginal drainage. Some

subside spontaneously. (2) Secondary abscess in the left iliac fossae; usually satisfactory drainage through the rectum; rarely, an abdominal drainage is required. (3) Abscess between the liver and transverse colon; difficult to detect; the majority will subside; at times, drainage through subcostal incision is indicated. (4) Infection of subphrenic space is the least common; some may subside without recognition; only 1 case in this series required surgical drainage and 2 others were found at autopsy.

Miller and his associates<sup>25</sup> classified over 1000 cases in children into 3 groups:

1. All cases of acute appendicitis before perforation: Of these 629 had immediate appendectomy without a death.

2. A group with symptoms of longer duration, but not the anxious facies, and with a definite palpable localized mass. These represent the abscess group with slow perforation and adequate defense response. Of 228 patients in this group, 25 were operated for drainage, but it was felt that some would have subsided without surgical intervention. The remaining 203 were given the benefit of watchful conservatism, and 198 recovered: a mortality of 2.5 per cent. These patients are advised to return in 3 months for an appendectomy. In the few cases with progressive enlargement of the mass (a true abscess) extraperitoneal or rectal drainage, depending upon location, is advised.

3. Cases of acute perforation into the peritoneal cavity, against which there is inadequate defense. The patients are very sick; with pinched, anxious expression; a dry tongue; a rapid pulse; variable fever and leukocyte count; knees flexed; thoracic breathing; abdominal distention, rigidity, and tenderness of generalized type; and absent peristalsis. The picture of

spreading peritonitis. Of 306 cases in this group, 25 were treated conservatively with a mortality of 80 per cent; the remaining 281 were given the benefit of immediate operation with 242 recoveries, or 12.8 per cent mortality. In the past 2 years all patients in this group were operated on, no matter how much time had followed perforation. The technic for this group was almost always a McBurney incision, suction instead of sponges, delivery of appendix with Babcock forceps, ligation of the stump with inversion if possible, soft cigarette drains to the source of infection, especially if the retroperitoneal space is invaded.

In discussing this paper, Stone<sup>26</sup> agrees with the above treatment with the following modification: Appendicitis with abscess formation need not necessarily be operated upon immediately. He emphasized the importance of being certain that the appendix would be removed subsequently, or better still before the patient left the hospital. Stafford and Sprong,<sup>22</sup> reporting from Johns Hopkins, recommend immediate operation for all types of appendicitis.

The Horsleys<sup>27</sup> are strong advocates of immediate operation and removal of the appendix in all cases of appendicitis.

Gatch and his associates<sup>28</sup> studied the reports of 656 consecutive cases of appendicitis in children under 16 years of age. These were divided into (a) 357 cases without gangrene or suppuration, no deaths; (b) 164 cases with gangrene or suppuration without perforation or with early perforation, no deaths; (c) 135 cases with gangrene and perforation or with perforation and abscess, 2.9 per cent mortality. The practice followed was an *immediate operation*, after several hours of study and preparation by *continuous gastric lavage*, intravenous injection of 5 per

cent *glucose in normal saline*, or in some cases a *blood transfusion*. Of the 135 advanced cases, 119 had an immediate operation. A gangrenous or perforated appendix was removed in 112 cases, while the other 7 had surgical drainage of the abscess without appendectomy. Autopsy showed that septicemia and ulcerative endocarditis caused the only death in this series, a mortality of 0.83 per cent. This was contrasted with a mortality of 18.7 per cent for the 16 children treated conservatively. The 3 deaths were due to peritonitis, although the children were not more seriously ill than those who had immediate operation.

The authors advocate a McBurney incision of adequate size, gauze only to facilitate exposure, location of the appendix and evacuation of abscess by suction, removal of appendix if possible, ligation with inversion of the stump if the cecum permits, exploration of the pelvis and lumbar gutter for pus, Penrose tubes without gauze into the pelvis and lumbar gutter or as a cofferdam around the head of the cecum, interposition of omentum between the drains and intestine; and loose abdominal closure.

It is pointed out that the pathological, the physiological, and the chemical changes which occur in peritonitis resemble those which follow a total cutaneous burn. The surface area of the body and peritoneum are about equal. Both respond to irritation by inflammation and exudation. Most of the toxic symptoms of peritonitis are due to loss of blood protein through damaged capillary endothelium with a resultant fall in osmotic pressure, blood concentration, and tissue edema. Injudicious administration of water in the presence of peritonitis dilutes the blood protein and increases the hypoprotein-

emia. The authors are convinced that the free use of *blood transfusions* has been a significant factor in the low mortality which they report.

In an analysis of 100 cases of *perforated appendicitis* Jackson and Perkins<sup>29</sup> report a 12 per cent mortality. They feel that it is better to operate as soon as the patient's condition permits, and to remove the appendix rather than merely establish drainage. If, however, perforation is days old and either spreading peritonitis or localizing of an abscess is occurring, immediate operation is contraindicated. In such cases the time of operation must be determined in each case. They prefer the paramedian incision in most cases. *Spinal anesthesia* seemed to have been a definite factor in reducing the mortality; of 33 patients who had gas and ether, there were 6 deaths, while 40 patients had spinal anesthesia with only 2 deaths.

**Delayed Operation**—Haggard and Kirtley<sup>30</sup> believe that it is a mistake to subject patients with a spreading peritonitis to immediate operation, and that better results will follow the delayed or conservative treatment. They recommend: (1) Nothing by mouth; (2) *Wangensteen drainage* with a Miller-Abbott type of tube for distention; (3) from 5000 to 8000 cc. of 5 per cent *dextrose* in saline, keeping the urinary output up to 1500 cc. in 24 hours; (4) *complete rest of the intestinal tract* for 5 to 7 days; (5) small *blood transfusions*; (6) *oxygen mask* to minimize distention; (7) *Fowler's position*; (8) *hot fomentations* or an *icecap to the abdomen*; (9) *morphine* to increase the tone of intestine and prevent an adynamic ileus. To complete this outline it is advisable to mention the administration of *adrenal cortex extract* and the subcutaneous infusion of an 0.8 per

cent solution of *sulfanilamide*, as mentioned by Barrow and Ochsner.<sup>24</sup>

Many patients will improve under this treatment. The inflammatory mass will resolve or result in a definite abscess which may be drained on the twelfth or fourteenth day. If resolution occurs, the appendix should be removed 8 weeks later.

In cases, however, where the temperature and pulse do not subside, where the mass increases in size, or where the pain increases in severity despite careful treatment, immediate operation is indicated. Drainage of an abscess alone is preferred if appendectomy necessitates breaking down nature's barriers.

In this series of 2613 cases there were 83 deaths, or 3.1 per cent mortality; these were divided into 2007 cases of acute appendicitis with a 0.54 per cent mortality, 417 cases of localized peritonitis or abscess with 5.7 per cent mortality, and 189 cases of generalized peritonitis with a 24.8 per cent mortality.

*Appendiceal Abscess*—In a series of 212 cases of appendicitis, Arnheim and Neuhoof<sup>31</sup> report a mortality of 1.8 per cent; however, there were only 13 cases with diffuse peritonitis with a mortality of 23 per cent. No deaths occurred in 40 cases of appendicitis with abscess or in the 17 cases of acute appendicitis with local peritonitis. The choice of time for operation in acutely ill, dehydrated adults is discussed with emphasis on deferred operation in the presence of proved diffuse peritonitis (proved by abdominal puncture).

Important features in the management of appendiceal abscess were: (1) Deferred operation in the early stages of appendiceal abscess and operation when the acute manifestations have subsided, except in infants and children; (2) at

operation, complete exposure and walling off of the abscess by packs; (3) entry of the abscess through a plane of cleavage which is developed progressively; (4) complete evacuation of all recesses of the abscess or abscesses; (5) meticulous "no touch" technic; (6) removal of the appendix in most instances; (7) drainage of all recesses of the abscess cavity or cavities by gauze packs, and not by tube or rubber dam. There was an absence of profuse or malodorous discharge following this technic. A transient fistula occurred in 1 case. No incisional hernia was observed.

*Sulfanilamide*—Ravdin, Rhodes and Lockwood<sup>32</sup> report that the mortality in a series of 809 consecutive cases of acute appendicitis has been reduced from 1.5 per cent in the first 552 cases to 0.4 per cent in the last 257 cases. The improvement is attributed to the use of sulfanilamide in all severe cases in the latter group. No other factor was changed in the 2 series. The degree of reaction in the patients with extensive peritoneal infection was less marked in the group treated by sulfanilamide. Animal experiments show that the drug readily diffuses into the peritoneal cavity, indicating that the peritoneum is a favorable site for action. The character of the lesion is more important than the specificity of the organism in determining the effectiveness of the drug. Intestinal obstruction was not encountered since suction drainage had been used.

*Method of Administration*—In patients with peritonitis extending beyond the operative field, sulfanilamide was given in 0.8 per cent concentration in physiologic saline solution by hypodermoclysis. Usually 2 drams (8 Gm.) are given the first day, reducing this by 15 grains (1 Gm.) daily, according

to the patient's response. In milder infections,  $1\frac{1}{2}$  drams (6 Gm.) by mouth the first day, gradually reducing to  $\frac{3}{4}$  dram (3 Gm.) over 4 to 7 days, then stopping. The daily dose is divided into 4 installments at 6-hour intervals. The blood sulfanilamide should be maintained above 5 mg. per cent; in some cases it has exceeded 15 mg. per cent. Complete blood counts every 24 to 48 hours, to determine a rapid anemia or leukopenia, are indicated. Among the toxic reactions observed, hyperpyrexia, with or without tachycardia or leukocytosis, was the commonest; this was seldom observed before the fourth day, and in the convalescing patient was considered an indication to stop the drug. Cyanosis was observed also, and must be distinguished from the cyanosis of failing circulation.

The other factors considered are the following: (1) Operation as soon as possible in all cases except the few which arrive late with a tendency to localization or those with abscess. Except in clear-cut cases of appendiceal abscess, which need not be regarded as emergencies, operation was delayed in less than 2 per cent of the cases. (2) Spinal was the anesthesia of choice; patients under 15 had open drop ether. (3) A McBurney incision was used, and enlarged as required. (4) The appendix was removed regardless of its pathology, except where a definite abscess wall would have been destroyed in doing it. In occasional cases with marked cecal induration a catheter was fixed at the stump. (5) Fibroplastic exudate on surfaces other than the appendix itself, gross fecal contamination, and frank pus were regarded as indications for drainage. Iodoform gauze packing covered with sheet rubber dam to the appendiceal site, a cigarette to the lateral gutter, and a cigarette and soft tube to the pelvis were used. (6) Post-

operatively, nothing by mouth or rectum; *suction drainage* prophylactically; no prostigmine or pitressin during the first 3 days; routine administration of *morphine sulfate* on empiric grounds; *fluids intravenously* with *serum protein* and *serum chlorides* every 48 to 72 hours; *transfusions of citrated blood* for anemia, hypoproteinemia, and patients with a rapid pulse and peripheral vasoconstriction.

The case of a premature infant weighing 3 pounds 12 ounces successfully recovering from a Rammstedt operation, and 8 months later from an acute perforated appendicitis with abscess formation was reported by Vickers and Conrad.<sup>33</sup> The appendix was removed.

King<sup>34</sup> believes *bacteriophage* (cololysate, Lilly) has been a valuable adjunct in the treatment of the complicated cases of appendicitis. The total number of cases was only 28, which is too small for a definite opinion, but continued use for evaluation is suggested.

### Chronic Appendicitis

An analysis of the end-result of 385 patients who had submitted to appendectomy at their homes was made by Alvarez.<sup>35</sup> He found that cure was obtained in only 2 of 255 who had never had an acute attack, while 87 of 130 who had at least 1 acute attack of pain were cured. If the fair results are added, the figures are increased to 4 and 92, respectively. The commonest reason for operation in the group which obtained a poor result were chronic fatigue, nervous breakdown, or a psychopathic makeup. Other reasons were duodenal ulcer or ulcer-like symptoms, migraine, functional diarrhea, sensitive colon, nervous regurgitation, gall-bladder disease, a sore liver, spondylitis, food sensitiveness, renal colic or constipation.



The definite *indications for an interval appendectomy* are: (1) A patient who has had 1 or more attacks of what resembled acute appendicitis, followed by indigestion, loss of energy, toxic feelings, a sore cecum and perhaps cramps; (2) appearance of these symptoms in a youth or girl who had been previously well. Occasionally an ulcer-like syndrome is due to chronic appendicitis. To this, x-ray evidence of fecoliths should be added.

#### **Technic of Interval Operation—**

An oblique lower right abdominal incision which cuts all the layers in the same direction (including the internal oblique and transversalis) is described by Saint.<sup>36</sup> This incision is not new and was used by Morrison about the same time that McBurney described his muscle-splitting incision. The advantages given are (1) ample exposure; (2) dependent and efficient drainage; (3) the lateral approach is ideal for retrocecal, retrocolic and appendiceal abscess; (4) no greater incidence of hernia.

Experimental appendectomies were performed on rabbits by Kross<sup>37</sup> in an attempt to determine the best method of handling the stump. The stump was buried in 23 and in 16 simple ligation was employed. Gross and microscopic examinations were made at intervals up to 90 days. Hemorrhagic infiltration and ulceration of the mucous membrane distal to the pursestring was a striking feature. In the unburied cases these features were absent. The buried stump cases showed a mesenteric lymphadenitis which was not observed in the cases with simple ligation. Adhesions were present in all cases but most marked when the stump was inverted. These studies point clearly and definitely to ordinary ligation (without inversion) as the simplest, safest, and most effective

procedure in the treatment of the appendiceal stump.

#### **Appendicitis in the Aged**

Stalker<sup>38</sup> studied a series of 82 cases of acute appendicitis occurring in individuals more than 60 years of age. These were seen at the Mayo Clinic from 1924 through 1938. There were 33 women and 49 men. Seventy were between 60 and 70 years and 12 between 70 and 80 years. Perforation was observed in 51 cases; of these, appendectomy was done in 26, and simple drainage in 20 cases; 8 of these had subsequent appendectomy. Conservative treatment was instituted in 5 cases of perforation. There were 13 deaths: 9 in the perforation group, in 5 of these the appendix had been removed; in 2, simple drainage; and 2, conservative treatment.

In the majority of cases the patient had mild cramp-like, intermittent general lower abdominal pain, which was associated with a mild indescribable dyspepsia and constipation. A laxative or enema was used to overcome constipation. There was a tendency to localization in the lower right abdomen. Temperature and pulse are only slightly increased. As the condition progresses, the pain becomes more severe and distention becomes apparent.

The *treatment* of uncomplicated cases is by **appendectomy**; in cases with recent perforations and no localization, appendectomy if possible without too much shock, trauma, or interference with nature's defense. The highest mortality occurred when appendectomy was done in the presence of peritonitis. **Ochsner treatment** should be followed in late cases of perforation and peritonitis. This is followed by simple **drainage** or allowing the mass to absorb. If the condition warrants, an appendectomy in 6 to 12 weeks is indicated.

to the patient's response. In milder infections,  $1\frac{1}{2}$  drams (6 Gm.) by mouth the first day, gradually reducing to  $\frac{3}{4}$  dram (3 Gm.) over 4 to 7 days, then stopping. The daily dose is divided into 4 installments at 6-hour intervals. The blood sulfanilamide should be maintained above 5 mg. per cent; in some cases it has exceeded 15 mg. per cent. Complete blood counts every 24 to 48 hours, to determine a rapid anemia or leukopenia, are indicated. Among the toxic reactions observed, hyperpyrexia, with or without tachycardia or leukocytosis, was the commonest; this was seldom observed before the fourth day, and in the convalescing patient was considered an indication to stop the drug. Cyanosis was observed also, and must be distinguished from the cyanosis of failing circulation.

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**Treatment**—This is *surgical removal*, in 1 or 2 stages. A cecostomy may be done as the first stage and a resection as the second. The Mikulicz operation is probably the procedure of choice for tumors of the transverse, descending or sigmoid colons. Lipomas of the rectum may be resected through a proctoscope.

### Simple Ulcer of Right Side of Colon

**Importance in Diagnosis of Abdominal Disease**—Harrison<sup>2</sup> presents a study of 6 instances of simple ulcer of the cecum and ascending colon. The etiology and pathogenesis is unknown. Perforation of the bowel occurred as a result of the inflammatory process in 4 of the patients. The diagnosis is difficult. Perforation of such lesions may simulate perforation of an acutely inflamed appendix or may exhibit and mimic appendiceal abscess. Differentiation from perforated duodenal or gastric ulcer may be difficult. The complications arising from simple ulcer of the colon give rise to a very high mortality. A correct diagnosis could not be made from barium enema plates.

### Sigmoidal Polyps

A careful study of the removed lesions of 827 cases of carcinoma of the colon or rectum by Cattell and Swinton<sup>3</sup> showed that 120 or 14 per cent could be proved histologically to have arisen from benign mucosal polyps.

**Symptoms**—In Cattell's 10 cases of sigmoid polyps, bleeding was the presenting symptom. In 6 instances the bleeding had been present for from 1 to 15 years. One patient had obstructive symptoms because of the size of the polyp.

**Diagnosis**—Proctoscopic and sigmoidoscopic examinations prove of the greatest value diagnostically. It is im-

portant to have the patient in the inverted position so that the rectosigmoid will become straightened by gravity and the instrument can be passed into the lower sigmoid. Barium enema and double-contrast air enema often will be necessary to demonstrate the discrete polyp.

**Treatment**—Those polyps below the pelvic peritoneal reflection can be *fulgurated* under direct vision. Those above the pelvic peritoneal reflection can be fulgurated successfully if great care is exercised to avoid perforation and bleeding. Cattell believes that all sigmoidal polyps should be *removed by laparotomy*. Polyps can often be palpated through the sigmoidal wall and moved back and forth through the lumen. After carefully walling off the segment of involved bowel containing the polyp, a longitudinal incision 3 inches long is made in the tenia-coli band. The polyp is excised with a generous portion of the mucosal base where the pedicle is free. The incision is next closed with fine silk sutures in 2 layers.

### Intestinal Cancer

**Etiologic and Pathologic Factors**—David<sup>26</sup> calls attention to the frequency of supposedly benign polypoid growths of the large intestine and their relation to cancer. His studies comprised 200 resected cancers and 100 specimens of supposedly benign polyps of the colon and rectum. One of the most common alterations in the mucosa of the colon is the occurrence of millet seed-sized flat elevations, which are usually multiple and occur mostly in old persons. The histologic structure of these lesions is that of simple hyperplasia with inflammation or lymphatic hyperplasia of the submucosa. In exceptional instances the lesion may resemble larger polyps, which are almost certainly tumors rather than

simple hyperplasia. The next most frequently seen type of polyp is the adenomatous polyp. It varies in size from that of a pea to that of a large cherry and may be transparent or of the same color as the mucosa. It has the indications of being a benign lesion.

Other polyps of this adenomatous group present evidence of a growth or tumor change in their epithelium; their color is plum or cherry. They may become large, with a cauliflower surface, and contain branching stalks of connective tissue. In this type of adenoma the mucosa has taken on real growth propensities; it is a benign tumor. Another gross division of benign polypoid tumors is that of papilloma or villous tumors. The tendency to wild, disorganized tissue growth is found in these tumors, and in 2 of 27 cases the author has seen an early carcinoma beginning in the lesion. One of the most convincing arguments in favor of the relation of polyps of the large bowel to the development of carcinoma is seen in multiple polyposis, in which the entire colon and rectum may be studded. The etiologic basis here is heredity. They have a tendency to malignant degeneration.

Akin to this lesion, but lacking the hereditary factor and the extensive involvement, is the occurrence of *multiple polyps*. It seems probable that the malignant degeneration of these polyps is responsible for the increasing recognition of multiple cancers of the large intestine. The author observed 5 double cancers of the large intestine, in 4 of which the condition was highly suggestive of carcinomatous degeneration of polyps. Of less importance are the so-called lymphoid polyps, which may appear as multiple, slightly elevated, flat lesions a few millimeters in diameter, affecting the colon and rectum, and really a form of lymphoid hyperplasia.

Of more clinical interest but lacking carcinomatous tendencies are the *large lymph polyps*, of which the author has seen 5 instances in the rectum. The last classification is the inflammatory type. The elevations and tumor-like growths on the mucosa of a patient with this type of polyp ranged from simple hyperplasia to typical adenoma formation. The author concludes that there is a gross and gradual histologic transition in the mucosa of the large bowel from hyperplasia to adenoma or from papilloma to carcinoma. Whether the tendency to carcinoma is present from the start is not known. Carcinomatous changes can be diagnosed only by gross evidence of induration or ulceration and by microscopic evidence of invasion. While many of the polyps of the colon remain benign for years, they cannot be trusted to do so and should be thoroughly removed, locally if benign, and radically if malignant. The results of biopsy are not conclusive unless the material is taken from an area of ulceration or induration. It is frequently impossible to make a diagnosis of malignancy from a small piece of tissue. It is better to examine the whole tumor. The earliest carcinomas the author has seen in the large intestine were 1 to 2 mm. ulcerating lesions found in polyps.

### Acute Nonmalignant Perforations of Colon

**Etiology**—The commonest cause is one of the complications of diverticulitis, foreign bodies, acute elevation of intracolonic pressure by enemas, or the occasional "compressed air injury." Six cases are detailed by Koucky and Beck<sup>4</sup> to indicate that acute perforations of the colon occur often enough to warrant consideration of this possibility in all obscure cases of peritonitis.

**Symptoms**—In the early cases the peritonitis may be observed to originate about the descending colon, while in the late cases the picture is that of diffuse generalized peritonitis. The onset is sudden.

**Diagnosis**—X-ray studies, especially as regards the presence of pneumoperitoneum, are often of value. The use of the barium enema in colon perforations is contraindicated because of the chance of spill into the general peritoneal cavity.

**Treatment**—The treatment must depend upon accuracy in diagnosis. The subacute perforations or those with limited leakage are best treated conservatively. Attempts at closure would seem to be justified in some acute perforations. Perforations due to disease do not permit accurate closure, because of the marked inflammatory reaction about the opening. In these, some type of exteriorization may be indicated. Drainage of the damaged segment, with or without colostomy above, may be the method of choice. *Colostomy* without exploration or any handling of the perforated bowel has resulted in recovery.

### Mikulicz Operation for Right Colon and Rectosigmoid

**Adaptation**—The Mikulicz operation is advocated when removal of the lower 6 inches of the ileum, cecum, ascending colon, and about one-third of the transverse colon is indicated. It is generally agreed that *acute obstruction* calls for *preliminary cecostomy* or *colostomy*. R. F. Carter<sup>5</sup> considers this procedure superior to the end-to-side enterocolostomy and repair of the raw surface on the posterior abdominal wall, because of the following reasons:

(1) The best methods of joining the ileum to the colon and of the raw surface are still under debate; (2) their method of repair of the raw surface on

the posterior abdominal wall is adequate for the removal of the entire lymphatic area attached to growths in the cecum and ascending colon; and (3) prior to the use of this means for repairing this defect, the area could not be covered when an adequate drainage field was removed. Spontaneous closure of the fistula is enhanced by suture of the peritoneum close to the crushing clamps, so that the mucous membrane edges will tend to retract away from the skin edges when the clamps are removed. After the wound is closed and the crushing clamps are placed on the ileum and colon near the skin, formalin solution is injected into the exteriorized bowel to prevent deterioration of the specimen during the time it is left in place on the abdomen. On the second or fourth day the growth is removed, and a rectal tube is inserted into the ileum and held by a purse-string suture. The clamp on the colon is left in place to prevent intra-abdominal retraction. After the colon-crushing clamp is removed, the stoma clamp is applied deeply, and a tight ligature is passed around the open ends of the ileum and colon, the rectal tube remaining in the ileum; the protruding ends of the colon and ileum are thereby strangulated by this ligature. Thus, the open margins lie near the level of the peritoneum when the stoma clamps comes free, greatly facilitating healing of the stoma without secondary closure.

The authors' last 3 cases have closed spontaneously in from 8 to 12 weeks. The drainage of liquid feces is readily controlled in patients in whom there is primary union of the remainder of the abdominal wound. Adhesive tape is applied tightly across the edges of the wound over the open ends of the intestine.

The authors also describe their application of the Mikulicz procedure for *resection of the sigmoid colon and rec-*

*tum for carcinoma.* It is a combination of the Miles' resection and Kuttner's sacral anastomosis with preservation of the sphincters. The abdominal portion of the operation consists of mobilization of the mesosigmoid, ligation of the trunk of the inferior mesenteric artery below the left colic artery, and mobilization of the rectum down to the levator ani muscles. The abdomen is then closed temporarily and the patient placed in Sims' position. The growth is then delivered through a sacral incision through which the coccyx is first removed. The Mikulicz clamps must be applied without undue tension on the circulation of the loops. The patient is then placed on his back, the abdomen is reopened, and the peritoneal pelvic floor is closed. Three or 4 days later the growth may be removed, and the proximal opening is allowed to function as a sacral colostomy. The spur is crushed with an olive-tipped clamp after 5 or 7 days.

The most important factor in the after-care is to promote voluntary *closure of the sacral fistula*. This is done best by keeping the margins of the mucous membrane away from the skin by packing the cavity with gauze. Operative freeing is necessary when the mucous membrane and skin unite. Attempts to close the fistula after the first 3 or 4 weeks have all resulted in a breakdown of the suture line. When this is attempted, the sphincter must be divided. The authors report 8 patients operated upon since 1934, with 1 death from peritonitis. The other 7 patients are free of recurrences and all have normal movements, although 3 have sacral fistulas. Two patients have had dilatations of the sphincter for stricture.

**Results**—In W. J. Mayo's report on 262 resections of the large intestine for carcinoma, there were 5-year cures in 54 per cent of the patients who survived operation. Most of the operations were

of the Mikulicz type. A summary of the reports of Hockenegg, Anschuetz, Peterman, Moszkowicz and Mikulicz show that of 79 operative survivors, 20 are known to be dead of recurrence; 36 are known to be living and well. The report from the Roosevelt Hospital, New York, includes 63 cases in which a carcinoma of the large bowel was resected by the Mikulicz method. There were 12 deaths, an operative mortality of 19 per cent. Of the 51 operative survivors, 9 are known to have died of recurrence. A critical review indicates that 20 or 54 per cent of these patients were apparently cured by the Mikulicz type of resection.

### Cancers of Left Colon

**Delayed Resection After Exteriorization for Segmental Resection of Colon**—Quénu and Lignon<sup>6</sup> state that in 65 cases of cancer of the left colon which were operated upon, exteriorization of the involved segment of the colon and resection after a delay of several days were done in 14 cases. The technic employed was that of E. Quénu, as described by Cruet in 1914. In 38 cases no resection operation was attempted on account of the extent of the lesion. In 27 cases resection was done by other methods; in 11 of these the cancer was in the rectosigmoidal area, in which naturally there is no possibility of exteriorization. The technic used in the 14 cases involved 3 stages. In the *first stage* the segment of intestine which was the site of the tumor was exteriorized; the 2 layers of the mesocolon, left and right, were sectioned without injury to the blood-vessels or glands; each of these layers was sutured to the corresponding surface from which the parietal peritoneum had been separated. Sutures were placed around the vascular pedicles. The afferent and efferent loops

of the exteriorized segment were sutured in the incision in the abdominal wall, and compresses were placed around the exteriorized segment. In this way the intestinal segment was outside of the abdominal wall, and the vasculolymphatic pedicle outside of the peritoneum. In the *second stage*, from 5 to 7 days after the first, the sutures placed around the vascular pedicle were tightened to secure hemostasis and the segment of intestine and vasculolymphatic pedicle were sectioned. The 2 ends of the intestine were partially sutured in their posterior circumference. In the *third stage*, after varying intervals, the artificial anus was completely closed by suture of anterior circumference of intestinal segments.

All of the 14 patients operated upon by this method made a good postoperative recovery, without complications, although one-half were more than 60 years of age. This indicates that the operation is unusually well tolerated, and this is because it is entirely extraperitoneal. In the first stage neither the intestine nor the vasculolymphatic pedicle is cut; the space in which this operation is to be done is merely prepared. By delaying the resection operation, the intra-abdominal, but extraperitoneal, surface partially heals; its walls are covered with fibrin and later with granulations; at the base of this cavity is the intestinal segment and its vasculolymphatic pedicle. They also are covered with granulation tissue; thus, the intestine can be opened and the lymphatics sectioned without danger.

The means of hemostasis are provided by the sutures placed in the first-stage operation, and there is very little bleeding. The first stage is the most important in this operation. In 2 of the cases included among the 38 in which resection was not done, the exteriorization of the colonic segment was carried out, but the

patients died. In 1 of these cases the tumor of the colon was found at operation for a malignant ovarian tumor and a subtotal hysterectomy was done before the exteriorization of the colon. Death was due to bronchopneumonia and is to be attributed to the hysterectomy rather than to the exteriorization of the colon. In the second case, the tumor was very large and infected; in the process of mobilization, which was difficult, some of the infected glands broke down, and caused peritonitis. This case was definitely inoperable. As no resection of the colon was done in these cases, they have not been included in the authors' statistics of colonic resection. If they are included in the exteriorization operations, the mortality is 12 per cent (2 deaths in 16 cases). If they are not included, there was no postoperative mortality in 14 cases.

Of the 14 patients who were discharged from the hospital after operation, 1 could not be traced; 1, a woman 62 years old, with Pott's disease and hemiplegia, died suddenly 2 months after discharge. Of the remaining 12, 6 died from 2 to 9 years after operation. In 2 of these cases death was certainly not due to recurrence of the cancer of the colon; in another case, death was probably not due to recurrence. In 2 cases death was known to be due to recurrence, and in a third case was probably due to recurrence. These 3 deaths all occurred in the course of the second year after operation. Of the 6 surviving patients, 4 are living and free from recurrence more than 2 years after operation, the 2 other patients less than 2 years. In all of these living patients, the artificial anus has been successfully closed.

### Intussusception

**Radiological Study**—The signs from the barium enema are as follows: (1)

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tain, the enema will provide a valuable therapeutic method in all but advanced cases and may render an operation unnecessary, or, if one is necessary, make it easier. (3) A wider use of roentgenological investigation in intussusception is clearly justified.

### **Permeability of Intestinal Wall for Bacteria, Especially in Circulatory Injury of Colon**

By means of animal experiments the attempt was made to determine under what conditions and at what time the colon, injured by interruption of the vascular supply of the mesocolon and ligation of the mesentery, becomes permeable for bacteria. After division of 1 or several blood-vessels in the ascending mesocolon by means of a median laparotomy in adult rabbits, the abdominal cavity was again opened at another site 12 hours after the operation under the strictest asepsis, and then smears from the surface of the serosa were made every 2 hours up to 24 hours for the bacteriological investigation. The findings were as follows:

Relatively often, directly after the operation, bacteria (mostly the *Staphylococcus albus*) were demonstrated on the surface of the serosa both in smears and culturally; these were considered to be of ectogenic nature. They were introduced at the operation and were no longer demonstrable after 12 hours. With the division of a blood-vessel of the ascending mesocolon, a partial necrosis of the intestinal wall frequently resulted within 24 hours. During this time, however, bacteria did not penetrate through the intestinal wall into the free abdominal cavity. If 2 blood-vessels of the ascending mesocolon were divided, complete necrosis of the intestinal wall resulted soon after 14 hours, and within from 14 to 16 hours after the operation

intestinal bacteria were already present on the intestinal serosa. They increased in number with the passage of time and could be demonstrated abundantly after 24 hours. In various cases, however, the surface of the serosa of the necrotic intestinal wall remained perfectly sterile. There was no basic difference between the conditions following the ligation of 2 and of more than 2 blood-vessels of the ascending mesocolon. Necrosis of the intestinal wall and penetration of the intestinal bacteria occur somewhat earlier (10 to 12 hours) with the division of more than 2 blood-vessels. By means of histological investigations, it was shown that the penetration of the bacteria, which always follows the onset of the necrosis early, occurs essentially by way of the lymphatics. The blood-vessels always remained free of bacteria.

Huruya believes that the possibility of the penetration of the intestinal bacteria is generally overestimated. With slight injury of the tissues, the necrosis of the intestinal wall as a result of section of the blood-vessels of the mesocolon with ligation of the mesentery definitely does not always injure the intestinal wall uniformly in its entire thickness; sometimes it is injured in its entirety and sometimes only in certain areas—the penetrating bacteria could never be demonstrated in the acute experiment. The kneading and massage of the portion of the intestinal wall separated from the mesocolon also could never bring intestinal bacteria into the abdominal cavity within 4 hours.

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## **SMALL INTESTINES**

### **Tumors of Small Intestines**

**Lipoma**—This is a benign tumor, generally submucosal, and at times subserosal. It is usually single and sessile,

*tum for carcinoma.* It is a combination of the Miles' resection and Kuttner's sacral anastomosis with preservation of the sphincters. The abdominal portion of the operation consists of mobilization of the mesosigmoid, ligation of the trunk of the inferior mesenteric artery below the left colic artery, and mobilization of the rectum down to the levator ani muscles. The abdomen is then closed temporarily and the patient placed in Sims' position. The growth is then delivered through a sacral incision through which the coccyx is first removed. The Mikulicz clamps must be applied without undue tension on the circulation of the loops. The patient is then placed on his back, the abdomen is reopened, and the peritoneal pelvic floor is closed. Three or 4 days later the growth may be removed, and the proximal opening is allowed to function as a sacral colostomy. The spur is crushed with an olive-tipped clamp after 5 or 7 days.

The most important factor in the after-care is to promote voluntary *closure of the sacral fistula*. This is done best by keeping the margins of the mucous membrane away from the skin by packing the cavity with gauze. Operative freeing is necessary when the mucous membrane and skin unite. Attempts to close the fistula after the first 3 or 4 weeks have all resulted in a breakdown of the suture line. When this is attempted, the sphincter must be divided. The authors report 8 patients operated upon since 1934, with 1 death from peritonitis. The other 7 patients are free of recurrences and all have normal movements, although 3 have sacral fistulas. Two patients have had dilatations of the sphincter for stricture.

**Results**—In W. J. Mayo's report on 262 resections of the large intestine for carcinoma, there were 5-year cures in 54 per cent of the patients who survived operation. Most of the operations were

of the Mikulicz type. A summary of the reports of Hockenegg, Anschuetz, Peterman, Moszkowicz and Mikulicz show that of 79 operative survivors, 20 are known to be dead of recurrence; 36 are known to be living and well. The report from the Roosevelt Hospital, New York, includes 63 cases in which a carcinoma of the large bowel was resected by the Mikulicz method. There were 12 deaths, an operative mortality of 19 per cent. Of the 51 operative survivors, 9 are known to have died of recurrence. A critical review indicates that 20 or 54 per cent of these patients were apparently cured by the Mikulicz type of resection.

### Cancers of Left Colon

**Delayed Resection After Exteriorization for Segmental Resection of Colon**—Quénu and Lignon<sup>6</sup> state that in 65 cases of cancer of the left colon which were operated upon, exteriorization of the involved segment of the colon and resection after a delay of several days were done in 14 cases. The technic employed was that of E. Quénu, as described by Cruet in 1914. In 38 cases no resection operation was attempted on account of the extent of the lesion. In 27 cases resection was done by other methods; in 11 of these the cancer was in the rectosigmoidal area, in which naturally there is no possibility of exteriorization. The technic used in the 14 cases involved 3 stages. In the *first stage* the segment of intestine which was the site of the tumor was exteriorized; the 2 layers of the mesocolon, left and right, were sectioned without injury to the blood-vessels or glands; each of these layers was sutured to the corresponding surface from which the parietal peritoneum had been separated. Sutures were placed around the vascular pedicles. The afferent and efferent loops

ascertains the distance between the tumor and the flexure. When the tumor is once found, it must be marked with the forceps and examination of the intestine should be resumed until the other flexure is reached. It must be remembered that frequently distended loops are encountered, which tend to bulge out of the abdomen. By this method of examination no lesion can escape examination, and as only a small portion of the intestine is exposed at a given moment, the organ suffers very little. The localization is perfect, each lesion can be examined, and the treatment can be decided upon with the best possible knowledge of the condition. In the case of intestinal tuberculosis in particular, the proximal obstruction is almost always the greatest one and the more important stasis and distention of the afferent loop are above it. The remainder of the intestine empty and flaccid may have important strictures which are easily overlooked. On the other hand a distal stricture may conceal other lesions in a distended proximal loop. In 1 of the cases (intestinal tuberculosis of tumoral form) the most important tumor was the lowest one and was seen only after the finding of 3 others. It also must be remembered that intestinal spasms may give a false impression of extension in a limited lesion (Reichel). As a matter of fact, these spasms are among the most common causes of failure in the most perfect end-to-end anastomosis.

**Treatment**—Once multiple intestinal obstruction has been found, the surgeon may follow 1 of 2 possible procedures, *i. e.*, (1) ~~resection~~ of the affected intestine; or (2) a **short-circuiting operation** which, leaving the tumor, re-establishes the continuity of the intestinal lumen. The *first procedure* is indicated in cases of suspected malignancy; it is very simple from a surgical standpoint.

Undoubtedly it is the most satisfactory procedure, but also the most dangerous for the patient. The coaptation of both ends may not be easy; a good method of overcoming the difficulty is to section the narrower loop very obliquely so as to adapt its lumen to that of the more distended portion, or a laterolateral anastomosis may be substituted, which is recommended in case the technic is not perfect. If a resection is performed, it is better not to resect more than 6 feet of intestine, in order to avoid disagreeable consequences.

The *second procedure*, the short-circuiting operation, requires 2 conditions, *i. e.*, (1) certainty that the tumor is benign; and (2) assurance that the multiplicity of the tumors will not provoke digestive troubles. The authors' second, third, and eighth cases were treated in this manner with satisfactory results. When a lesion has not reached the tumoral form, but its characteristics and the evolution of the other lesions indicate the possibility of such an eventuality, it must receive the same treatment as the tumoral form. This fact must be kept in mind when the type of operative procedure is determined. One of the authors' cases of tumoral tuberculosis had some simple hypertrophic infiltrations which were treated like the more advanced tumoral forms. The suture of the abdominal wall must be done very carefully, and a good strapping will avoid the tendency toward evisceration, which is very common in these cases. The Wangensteen method of preoperative and postoperative treatment of cases with serious obstruction was used with very satisfactory results. When an intestinal lesion of a definite nature is found, exploration is of great value, because, in addition to the first process, another of a different nature and which requires more active treatment frequently

can be found. This is true when, during the operation for intestinal syphilis, cancer is found also, which frequently co-exists with the former disease.

**Malignant Lesions of Small Intestines**—According to Mayo,<sup>24</sup> 108 cases of surgical malignant lesions of the small intestine were encountered at the clinic from 1907 to 1939, inclusive. This represents 1.5 per cent of the surgical malignant lesions of the stomach and 1.4 per cent of the surgical malignant lesions of the large intestine observed during the same period. The jejunum was affected most frequently. The ratio of multiple lesions to single lesions in the small intestine was about the same as that in the large intestine. The vast majority of these lesions occurred among patients whose average age was 52.6 years. This pathologic change occurred about  $2\frac{1}{2}$  times as frequently among men as among women.

The actual or tentative diagnosis of a malignant lesion of the small intestine was made in 25.7 per cent of 101 cases. It seemed to have been somewhat easier in cases in which the growth occurred in the jejunum and duodenum. The 2 main features which stood out were recurrent attacks of intestinal obstruction with intercurrent relief and anemia, weakness and fatigability. A careful history will often reveal the fact that these later symptoms antedate the gastro-intestinal complaints. Loss of weight, although constant in the late stages, is inconstant early in the disease, as is also constipation.

It could be assumed that the higher the lesion is in the intestinal tract, the more quickly will the symptoms present themselves. This is not the case. Barium sulfate orally for x-ray examination in the presence of obstruction in the small or large intestine is inadvisable. With the advent of the Miller-Abbott tube for

intestinal decompression, barium sulfate in fine solution could be used and the portion of intestine proximal to the site of obstruction can now be satisfactorily cleansed prior to operation, but close attention and careful effort by competent physicians are essential. The roentgenogram, when it signifies the presence of a lesion of the intestine, reveals evidence of a narrowing or filling defect of the intestinal lumen at the site of the lesion and a compensatory widening proximal to the obstruction. The retention of barium sulfate in the small intestine for more than 8 hours should arouse suspicion of a pathologic lesion and stimulate further effort toward localization of the lesion, if compatible with the condition of the patient.

Surgical procedures in the 108 cases were carried out by 18 surgeons. When possible, *resection and re-establishment of intestinal continuity* was the operation of choice and the second choice a *palliative procedure and exploration*. *Closure* was employed only when the other 2 procedures were not applicable or were deemed to be without benefit. Resection (42.4 per cent) could be accomplished most frequently for lesions of the ileum; palliation (41.3 per cent) such as gastroenterostomy was the most usual procedure for malignant lesions of the duodenum; and exploration alone was possible in 16.3 per cent.

The typical malignant lesion of the small intestine is an *adenocarcinoma*, much the same ring constricting type that is frequently observed in the distal half of the colon. *Leiomyosarcoma* made up a little less than 10 per cent of the malignant lesions in this region. *Metastasis* first involves the lymph-nodes of the mesentery, then the peritoneum, liver, lungs, long bones and dura mater.

Of 85 patients operated on prior to January, 1938, 83 were traced and of

these, 25, or 30.1 per cent, survived for more than a year. Of 66 patients operated on prior to January, 1934, 65 were traced for 5 years and 8, or 12.3 per cent, survived 5 years or more.

Rodriguez and Schena<sup>25</sup> report a case of a *carcinoid* of the small intestine in a 37-year-old man. The tumor produced an intussusception. After a resection, a terminolateral anastomosis was performed with a Murphy button. As the pains recurred, and intestinal contractions became visible, a second operation was performed 6½ weeks later. Disseminated tumors were found in various locations between the duodenojejunal junction and the terminal portion of the ileum. After exteriorization of the tumor causing invagination, the abdomen was closed. The patient expired 2 weeks after the operation. The histological examination established the diagnosis of a carcinoid.

### Duodenum

**Duodenal Ulcer**—This is the commonest, most distressing and the most serious duodenal lesion. The Lahey Clinic has managed 3670 patients with duodenal ulcers. Only 8.2 per cent of the patients were operated on because of incapacitating symptoms. Lahey knows of nothing which has been of greater value in the care of patients with peptic ulcer than medical opinions concerning preoperative preparation and the separation of cases into those desirable for surgery and those not requiring surgery.

**Pathogenesis**—The gastroscopic findings of Christiansen<sup>8</sup> in patients with duodenal ulcer stress the disagreement between the gastroscopic and the pathologic-anatomic concepts of the pathogenesis of peptic ulcer. Konjetzny maintains that chronic ulcer is the end-product of a primary chronic gastroduodenitis which passes through the catarrhal and

the erosive stage, reaching its climax in the ulcerative stage with the formation of 1 or more chronic ulcers. In contrast to this view, Schindler and other gastroscopists consider chronic peptic ulcer and gastritis as 2 different lesions without causal connection. Gastroscopy in most cases of chronic ulcer does not reveal gastritis. Gastritic alterations which may appear in cases in which the ulcer gives rise to retention of stomach contents are secondary and curable. Ulcerations may appear in primary gastritis but they do not develop into chronic ulcers, since they are acute and transitory phenomena.

Christiansen found 70 cases of roentgenologically verified duodenal ulcer among more than 500 patients with organic lesions of the digestive tract. In none of these was it practicable to ascertain by relief examination changes in the stomach. The patients were examined gastroscopically at a time when they had pronounced dyspeptic symptoms and prior to the institution of treatment. Most of them were submitted to gastroscopic examination several times. He found that, regardless of the secretory conditions, gastroscopy demonstrated definite changes in the mucous membrane in 49 of the 70 cases (70 per cent) while the gastroscopic aspects were normal in 21 (30 per cent). Thus, in contrast to the opinion of Schindler, the gastroscopic examination revealed that the stomach in the majority of the cases was the site of pronounced pathologic alterations. The frequency of gastritis in duodenal ulcer cannot, however, be taken to confirm the observations of Konjetzny, as there is a considerable difference between the changes observed and those found in resected specimens.

The author reviews a case history which furnishes an explanation of the divergence between Konjetzny and Schind-

ler. If resection had been performed on a patient when his illness was at its worst, the specimen would have presented the picture on which Konjetzny based his theory. There would have been a duodenal ulcer associated with a violent, erosive, antral gastritis. The course of the disease showed, however, that these pronounced changes were of an acute character, healing within a few weeks when the pyloric spasm subsided and the retention disappeared. Improvement of clinical symptoms ran parallel with rapid healing of severe gastric changes, while the roentgenographic changes in the duodenum remained constant. This may be interpreted as indicating that the particular duodenal ulcer is the primary lesion while gastritis is secondary.

The author believes that, as a general rule, patients with a nonstenotic duodenal ulcer are liable to pathologic changes in the gastric mucosa even though no abnormality may be demonstrated by roentgenography or the Ewald test meal. Gastroscoy is the method of examination capable of settling this question. The gastritis may be total or partial. The erosions are acute manifestations which may heal in a few days, regardless of whether the gastritis improves at the same time. Transition to a chronic gastric ulcer has not been observed. The typical ulcer symptoms seem to appear in cases in which the stomach is affected. Acute gastric retention may be associated with severe erosive changes in the stomach. These changes are inconstant and may disappear rapidly when the retention subsides. Probably this condition does not involve a primary gastritis, as has been claimed by Konjetzny, but more likely secondary peptic injury, as asserted by Schindler.

**Treatment**—Lahey feels strongly that the selection of the type of operation for

duodenal ulcer must always be made not in terms advocated by so many European surgeons, namely 100 per cent gastrectomies, but in terms of how well the individual will stand the operative procedure. Lahey did a *subtotal gastrectomy* for peptic ulcer in 296 cases. It includes the removal of three-fourths to four-fifths of the stomach. He gets rid of a large proportion of the acid secreting glands and puts back into the stomach by means of the anastomosed jejunum the alkaline jejunal contents. He has found that the patients who have the lowest values for acid have had the best results, the fewest recurrences of ulcer and the fewest digestive symptoms after operation.

Lewisohn<sup>9</sup> considers that *partial gastrectomy with removal of the ulcer* is the operation of choice for duodenal ulcer. Opposition to gastric resection persists because of technical difficulties inherent in the operative technic. He believes that if gastric resection was technically as simple as a gastroenterostomy or a pyloroplasty, every surgeon would employ it. Exaggerated statements have been made about the inherent mortality and the magnitude of the operative procedure in gastric resection. With some experience and with proper organization, the mortality in primary cases of gastroduodenal ulcers should not be higher than about 5 per cent. The mortality following a subtotal gastrectomy for gastric ulcers is usually higher than that following partial gastrectomy for duodenal ulcers. Yet gastric resection for gastric ulcers is considered by most surgeons as a justifiable procedure, whereas gastric resection for duodenal ulcers is considered too radical.

It appears that opposition to the procedure is due to some extent to the abuse of the term "subtotal gastrectomy." The term implies that only a small stump of

stomach is left. This term is fitting for the operation for high gastric ulcers. When duodenal or prepyloric ulcer is being dealt with, the removed part represents a little more than one-half of the stomach. Partial, rather than subtotal, gastrectomy is the correct term for this operation. The term "gastric resection" is also incorrectly applied to certain operative procedures. The surgeon should distinguish between a prepyloric or a postpyloric *Finsterer operation*. The Finsterer operation puts the ulcer at complete rest and reduces the preoperative hyperacidity considerably. Thus, the method has a sound principle. The same cannot be said of the palliative resection of Madlener. If temporary cures follow this method, they probably occur independently of the operation, not because of it.

Perforation and hemorrhage, the serious complications of duodenal ulcer, have been more frequent in recent years because duodenal ulcer is still considered a medical disease, even after repeated medical failures. The fact that a fair percentage of ulcer cases are refractory to medical treatment must be recognized. The economic factor may at times place the ulcer patient in the surgical group. While partial gastrectomy is far superior to gastroenterostomy or pyloroplastic operations, it is not a definite safeguard against a recurrence. The ideal method for permanent cure of chronic duodenal ulcer still has to be found and it is possible that it will be along medical lines. At present, when a series of medical treatments has failed, *partial gastrectomy* is the best method. It relieves the patients of many years of suffering, safeguards him against the serious complications of perforation or hemorrhage and effects a permanent cure in about 90 per cent of cases.

Sixty-four consecutive cases of chronic duodenal ulcer treated by *gastroenterostomy* were studied by Westermann.<sup>10</sup> The objections of the majority of surgeons at the present time to posterior gastroenterostomy in the treatment of chronic duodenal ulcer is based almost entirely upon the fact that it is so frequently followed by jejunal ulcer. The literature favoring gastric resection, however, shows no distinction between partial gastric resection and subtotal gastric resection. That partial resection is frequently followed by jejunal ulcer is already recognized, and subtotal resection is not immune to this complication. While subtotal gastrectomy is a satisfactory operation and fulfills the last requirement, its immediate mortality and postoperative complications, however, will never be eliminated.

The author cannot agree with the surgical teaching which recommends subtotal gastrectomy as the only procedure for cure of chronic duodenal ulcer. In the hands of those with less experience, smaller portions of the stomach will be resected and the mortality and immediate complications will be high without insurance of permanent cure. Gastroenterostomy is not a haphazard fistula between some part of the posterior gastric wall and the jejunum, but a definite well-planned, carefully-placed opening between a certain limited area of the stomach wall and a corresponding segment of the jejunum. Some of the important features are: (1) The stomach site falls along a line from the lesser to greater curvature drawn obliquely downward from left to right; (2) the lower angle of the stoma falls below a line bisecting the body of the stomach; (3) the serosa of the jejunum is buttressed to serosa of the stomach for an inch above the upper angle of the stoma; (4) the opening in the lesser sac is affixed to the

stomach wall above the stoma; (5) the jejunal site is arbitrarily taken to allow the jejunum to fall naturally without angulation when the stomach is replaced; and (6) the size of the opening will vary with the size of the stomach, but will not be less than  $1\frac{1}{2}$  inches in diameter. No clamps and no nonabsorbable sutures are used. All bleeding points in the stomach and jejunal walls are tied. Two sutures are used, 1 continuous for the serosa, and 1 of a self-inverting type for the mucosa. It is important not to place the stoma near the pylorus.

In the author's series of 64 consecutive cases there were 2 postoperative deaths (3.12 per cent): 1 followed wound disruption and a pulmonary complication following resuture of the wound; the second was secondary to obstruction of the distal jejunal loop from dense adhesions. The results were unsatisfactory in 5 patients (7.6 per cent). One patient developed a definite jejunal ulcer, which was proved at autopsy. It was possible to follow 54 cases continuously after operation. Thirteen of the patients were followed for 10 years or longer; 25 from 5 to 10 years; and 16 from 1 to 5 years. From the results obtained in these patients, the conclusion is drawn that posterior gastroenterostomy in the surgical management of duodenal ulcer has met the specified requirements essential to justify continuance of its use.

Brulé and his associates<sup>11</sup> report a case of ulcer of the second portion of the duodenum in which *gastroenterostomy* was successfully performed. Duodenal ulcers of the second portion are usually found between the upper bend and the ampulla of Vater. They are trebrant, affect the pancreas and are accompanied with serious manifestations of periduodenitis and pancreatitis. They often appear as huge tumoral masses with hyperemia of tissues and pronounced vasculariza-

tion. The authors stress the importance of a differential x-ray diagnosis directed to duodenal diverticula, to the dilatation of the ampulla of Vater, especially when it attains significant dimensions, and to certain bulbar ulcers, since in consequence of inflammatory reactions or adhesions the shape and contour of the bulb may be completely modified.

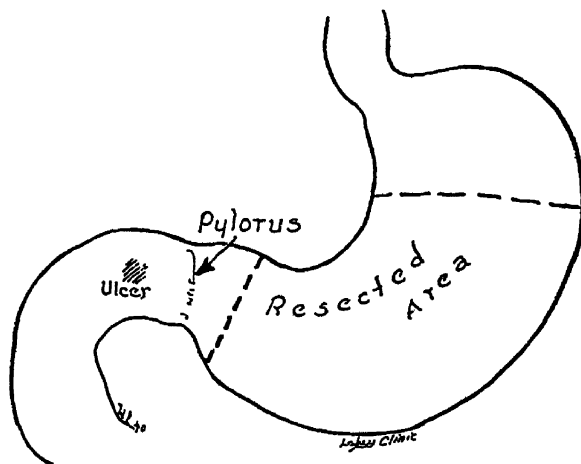


Fig. 1—Resection by exclusion (Finsterer). Area between dotted lines represents portion of stomach to be removed. Stomach is transected at prepyloric line and turned in, ulcer and pylorus remaining intact and unremoved. (Lahey. New England J. Med)

Complications in duodenal ulcers of the second portion may be due to stenosis of the bile-duct and duodenum, to pancreatitis and to perforation. Hemorrhages are frequent.

Demirleau<sup>12</sup> reports 4 cases of duodenal ulcers in which, on clinical and radioscopic examinations, *gastrectomy with exclusion* was performed. The age of the patients ranged between 28 and 56 years. In all patients gastric or epigastric pains had made their first appearance in early infancy (second or third year). In all 4 cases large ulcers were discovered in the second portion of the duodenum, 3 times with implications of pancreatitis. In 1 case a stenosis was found below the upper bend, large enough to prevent passage of a finger.



In another case the base of the ulcer was situated 2 cm. above the ampulla of Vater and the ulcer had eaten its way into the bile-duct, causing an opening of more than 1 cm. All cases had fatal endings, 3 from complications (pneumonia, peritonitis, pleurisy), the fourth from an involvement of surgical complications. Four necroscopic views with reduced replicas are shown.

Patients with duodenal ulcer developing obstruction can be put to bed, and under ideal conditions of rest and neutralization, an obstructed pylorus can be so relaxed that food will pass through quite satisfactorily. If these patients have 2 or more episodes of obstruction they should be operated upon. For patients with perforated duodenal ulcers a simple closure is done unless this produces obstruction. After the patient recovers from the perforation, he is placed under medical management and studied to determine whether the ulcer can be healed without operation. As to bleeding from a duodenal ulcer, it has been shown by Finsterer, Taylor and others, that if operation is performed on patients who are having massive recurring hemorrhages after 48 hours, the mortality will be almost prohibitive. If the surgeon expects to operate to surgically control the bleeding, it must be done within 48 hours.

**Diverticula**—Many duodenal diverticula do not produce symptoms of sufficient magnitude to justify operation. When erosion of the diverticulum begins, ulceration occurs. Then epigastric pain manifests itself. Distressing symptoms may come on as a result of accumulations within the sac. Diverticula appearing on the outer wall usually have their origin behind the duodenum, but can be approached by mobilizing the duodenum and turning it inward. At this point the common bile-duct enters the duodenum.

After the diverticulum has been cut off at its neck, care should be taken that inversion of the diverticulum does not obstruct the point of entrance of the common duct.

Diverticula projecting from the inner wall of the duodenum arise from the posterior wall and burrow into the head of the pancreas and into the vascular

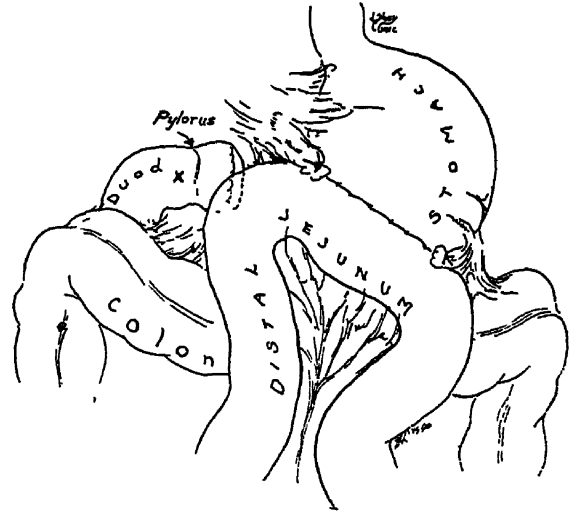


Fig 2—Resection by exclusion (Finsterer). Note duodenal stump, with ulcer removed, and stomach transected prepylorically and inverted. Also note high subtotal gastrectomy, with remainder of the stomach and high antecolic Hofmeister anastomosis. (Lahey. *New England J. Med.*)

structures at the angle made by the curve of the duodenum. Ducuing<sup>13</sup> reports a case of diverticulum of the duodenojejunal junction. The man was 53 years old and complained of epigastric cramps particularly severe 2 hours after meals. There was tenderness in the right hypochondrium and epigastrium. X-rays showed a triangular shadow connected to the duodenum at the duodenojejunal junction. The diverticulum was resected.

**Primary Duodenal Cancer**—Primary carcinoma of the duodenal bulb constitutes a well-defined anatomical and clinical entity among the epithelial neoplasms of the duodenum, which are

divided into those of the duodenum proper and those of the ampulla of Vater; the former are subdivided into supra-ampullar and infra-ampullar tumors. Various theories have been offered to explain the origin of duodenal cancer: Development in an aberrant island of gastric mucosa or pancreatic tissue, in an old diverticulum of the duodenum, in

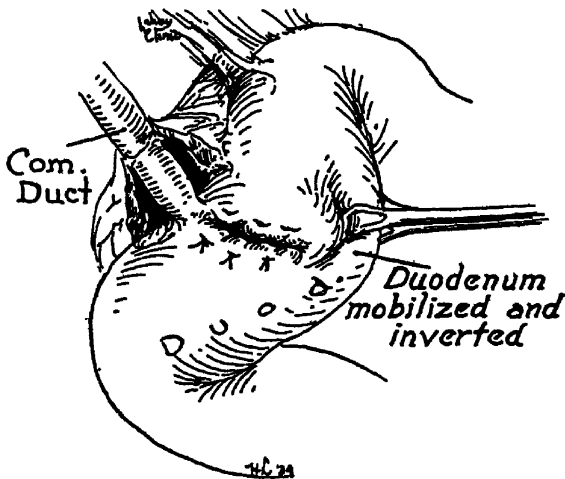


Fig 3—Removal of an external, safely removable duodenal diverticulum. Duodenum has been mobilized and inverted, and diverticulum cut off and its neck inverted. Note relation of origin of diverticulum to the point of entrance into duodenum of common bile duct. Care must be exercised lest inversion of the neck of sac obstruct the common duct. (Lahey: New England J. Med.)

a duodenal ulcer, or in Brunner's glands. The tumor is nearly always diffuse, annular, more or less stenosing, and infiltrating. The tumors may grow outward into the lumen as cauliflower growths, or may constrict the duodenal lumen by scirrhous annular infiltration of the wall. Histologically, it is an adenocarcinoma or an alveolar carcinoma. Various degenerations may occur, colloid degeneration being the most frequent; cystic cavities with a gelatine-like mucoid content are not infrequently found in the tumoral mass. The participation of the stroma in the tumor varies. The tumor nearly always contracts adhesions with

the neighboring organs, particularly the pancreas and the gall-bladder. Metastasis seems to be frequent, especially to the liver.

**Symptoms**—The clinical picture of carcinoma of the first portion of the duodenum is not characteristic and this explains the frequent errors in diagnosis. There are general symptoms, such as loss of weight and strength, nausea, vomiting, epigastric pain, anorexia, flatulent dyspepsia, and anemia. Pain in the right hypochondrium 2 or 3 hours after meals, accompanied or not by nausea and vomiting, occurs some time or other, and subicterus may be present. Hematemesis and melena are very rare. A choledochus syndrome appears in cases of compression of the biliary tract. At times the disease starts suddenly with great epigastric pain and symptoms recalling obstruction of the pylorus. Clinical examination offers nothing characteristic, but in some cases a tumor may be found on palpation, usually when the neoplasm has already invaded neighboring organs and contracted adhesions. Ascites is rarely present. Laboratory examinations offer no sure elements for the diagnosis. Theoretically, duodenal sounding may be of value; practically, it is not. The same applies to Roentgen examination. In advanced cases, the most frequent diagnosis is that of antropylic tumor. In short, the diagnostic difficulties are such as to make an operative diagnosis difficult or impossible.

**Differential Diagnosis**—Differentiation from carcinoma of the head of the pancreas can be made only when the latter condition has expanded the duodenal curve without producing mucosal erosion. Chronic pancreatitis may produce a similar x-ray picture. Infra-ampullary tumors produce duodenal stasis and may be confused radiologically with arteriomesenteric or extra-

luminal tumor pressure as from retroperitoneal lymph-nodes.

**Treatment — Surgery** is the only treatment to be considered. Unfortunately, many cases come to operation in the advanced stage and the immediate mortality is consequently high; in addition, recurrences are frequent within 4 or 6 months. In cases favorable from the surgical point of view, ample **gastro-duodenal resection** may give good immediate and late results. Lahey developed a new operative procedure that will well prove useful to anyone, who has to deal with gastrojejunal ulcer, with gastrojejunocolic fistula or with carcinoma high in the jejunum. As will be seen in Fig. 4, following the removal of an adequate amount of jejunum for carcinoma there was but a small stump of jejunum at the ligament of Treitz, with too short a mesentery and an intraperitoneal portion to permit safe end-to-end anastomosis. Even had it been possible, the anastomosis would have retracted retroperitoneally beneath the vascular mesenteric root, so that there would have been the distinct possibility of obstruction from pressure and the danger of leakage. After removal of the segment of high jejunum, both ends of the jejunum were inverted and reinforced with interrupted silk stitches.

The parietal peritoneum about the upper short stump of jejunum at the ligament of Treitz was then incised, and the stump was pushed beneath the vascular mesenteric root until it was on the opposite side of the mesentery. The incised ligament of Treitz was then closed and the entire right hepatic flexure was turned down by incising its outer leaf of peritoneum. This revealed the retroperitoneal duodenum and the mobilized upper stump of jejunum (Fig. 5). When this has been done, the mesentery of the retroperitoneal duodenum

and jejunum was of sufficient length so that when the transverse colon was put back in place the mobilized duodenum and jejunum could be passed over and in front of the transverse colon, the lower stump of jejunum would be brought up in an antecolic position and a safe lateral anastomosis could be accomplished between the antecolic mobilized duodenum and the jejunum (Fig. 6). The technical procedures are well illustrated by the line drawings.

This method has been of value also in cases of *jejunal ulcer*. When a jejunal ulcer occurs in a case of no-loop gastroenterostomy, the proximal loop of jejunum is so short after the segment of the jejunum containing the ulcer has been resected that safe end-to-end anastomosis cannot be done. In such cases, and in cases of gastrojejunocolic fistula, this plan of transposing the duodenal stump beneath the mesenteric root to the right side of the abdomen and then mobilizing the retroperitoneal duodenum has proved of distinct value.

#### **Chronic Obstruction of Proximal Duodenum by Congenital Bands—**

These bands are probably remains of the anterior mesogastrium. They cross the second portion of the duodenum from below and terminate in the region of the gall-bladder. Differential diagnosis is to be made between this condition and atresia of the intestine, and also between it and congenital pyloric stenosis. In the case of atresia, differential diagnosis is impossible preoperatively, but congenital pyloric stenosis can usually be differentiated from obstruction due to bands because of the fact that patients with the latter start vomiting after the first feedings, have bile in the vomitus, and present no typical olive-shaped abdominal mass. Because of flattening, constriction, and angulation of the duodenum due to the

bands, the proximal duodenum does not become dilated. The obstruction may be complete or incomplete, the former type requiring immediate operation, the latter usually pursuing a chronic course over many months or years with intermittent vomiting and chronic starvation. Operative technic consists of division of the bands on the outer, avascular margin of the duodenum. Preoperative and postoperative management is similar to that in cases of congenital pyloric stenosis except in the older patients.

**Retroperitoneal Traumatic Rupture of Duodenum**—Decoulx<sup>14</sup> found about 100 cases reported in the literature. The termination of such cases is usually fatal, especially if operation is late. Fixation of this portion of the bowel just in front of the spine renders it particularly vulnerable to injury. Incomplete ruptures not involving the mucosa may heal, but in most cases the mucosa is finally weakened and ruptures in a second stage. In complete ruptures the intestinal lumen is opened. In partial ruptures only a part of the circumference is involved by a mere puncture or a longitudinal or transverse fissure. Finally, the intestine may be cut in 2, as is usually the case in children. This form of total rupture is quite common (up to 22 per cent, according to Lenormant) in the intraperitoneal or extraperitoneal lesions, but most rare in the retroperitoneal type. Only 2 such cases have been reported.

The sites of predilection appear to be the extremities of the duodenum, the pyloric zone and the angle of Treitz. Only about one-fourth of the cases involve the third portion. The mechanism of the production of rupture varies according to the direction and form of the injury. Laceration is commonest in regions where the duodenum is fixed by solid attachments at the angle of Treitz

or the superior flexure. The intestine may be crushed against the spine, especially in its third portion, in which case the condition is usually associated with other lesions, particularly rupture of the pancreas. The commonest type of rupture seems to be that produced by bursting. The present case is the only one reported in which the rupture was due to a motor accident. Following rupture, the fluids escape into the cellular spaces, may detach the mesocolon, the mesentery, but in particular the pancreas, and flow into the perirenal region and even into the iliac fossa. The infiltration consists of food, biliary fluids, pancreatic juice, gas, and blood.

*Symptoms* are so atypical that a diagnosis is rarely made before the intervention. In spite of the absence of peritoneal inundation the clinical syndrome greatly resembles that of perforation peritonitis. The hourly acceleration of the pulse indicates a severe abdominal lesion. The facies becomes typical, but not until later. The disappearance of hepatic dullness cannot be counted upon because the peritoneum does not contain gas. Abdominal contraction is marked and early. The peritoneal symptoms do not appear immediately. There is often a free interval of from 5 to 6 hours, or several days, during which nothing indicates a serious lesion. The patient observed by the author walked a distance of several kilometers and slept several hours, the alarming symptoms not appearing until 8 hours after the accident. Other special symptoms which may develop are testicular pain, emphysema of the anterior abdominal wall, and deep prevertebral tumor.

Sperling *diagnosed* 1 case roentgenographically. If operation is not performed, death ensues within a short time. Only a very careful exploration at operation will prevent the oversight of such

a lesion. Diagnostic signs of aid include subperitoneal emphysema and a green spot in the submesocolic region.

**Treatment**—In the smaller punctiform ruptures the continuity of the intestinal tract may be restored by *lateral suture* with *linear* or *purse-string burial*. If the duodenal caliber is constricted, a *gastroenterostomy* may be required. In severe or total rupture, lateral suture becomes impossible. If the rupture is not total it may be necessary to complete it with excision of the entire bruised area. Opening of the 2 duodenal stumps to the skin or simple tamponade are merely procedures of last resort which usually fail. The digestive canal must be re-established by 1 of several possible methods: (1) End-to-end suture, which gave successful results in 1 case reported by Kantor but is too risky to be recommended; (2) closure of the upper end and opening of the lower end into the stomach; (3) closure of the lower end and opening of the upper end into the small intestine; and (4) closure of both ends with purse-string invagination. The last method is used in almost all cases. *Gastroenterostomy* is then required to restore the continuity of the intestinal tube. Other procedures found of use include *Finney's pyloroplasty* and the *complementary duodenojejunosomy* recommended by Guibe. Anastomosis may be accomplished more simply at the level of the pylorus by Delbet's technic of *gastroduodenojejunosomy*. If the rupture is located at the ampulla of Vater, operation becomes most difficult. Occasionally lateral suture is possible, but if the rupture is too extensive, a reimplantation of the papilla or even reimplantation of the pancreatic section into the intestine (Kausch) may be necessary. Even in the absence of such unfavorable conditions the long difficult operations required for

ruptures of the duodenum explain the poor prognosis of such accidents. Of 34 cases published by Rudolsky in 1927, only 5 terminated in recovery.

### Jejunum

**Primary Jejunal Ulcer**—Rufz is generally credited with calling attention to ulcers in the jejunum, having reported a case in 1843. Richardson collected 12 cases in 1922, and in 1924 Brown reported 35 cases of simple ulceration of the jejunum and ileum, 9 of which occurred in the jejunum. In 1933, Ebeling made a thorough study of the subject, surveying both domestic and foreign literature and presented a summary of the important findings in 47 cases, including 1 of his own. He omitted a case reported by Heinatz in 1928. Since then, Colletti has reported 2 cases and Puhl, Hall, Desjacques, Lastra, Smith, Harris, and Zemp have each reported a case in which there was a simple ulcer in the jejunum without ulceration in the remainder of the intestinal tract, and without any systemic disease or previous gastrojejunosomy. The detailed reports in recent years make it possible to outline certain findings that are present in the majority of cases which aid considerably in the diagnosis. The importance of this type of ulcer is readily appreciated when its mortality is reviewed. Of the 52 cases with sufficient data to be studied, 28 died, making a total mortality of 53.8 per cent. There were 43 perforated cases, of which 23 died, a mortality of 55.8 per cent. Twenty-five of the perforated group were operated upon with 9 deaths, or a mortality of 36 per cent. Those operated upon within 24 hours had a much lower mortality. There were 9 nonperforated cases, of which only 1 was correctly diagnosed before operation. All were operated upon with only 1 death, a mor-

tality of 11.1 per cent. The above mortality is considerably less than that observed 10 years ago.

**Pathology**—The upper one-third of the jejunum was by far the commonest site. Sixty-eight per cent were situated in its proximal portion. The majority (83 per cent) were opposite the mesenteric attachment, and varied in size from 2 mm. to 2 cm. and usually were single. Eighty-six per cent were circular in shape with a clean-cut, punched-out appearance, and on cross section were often terraced. This latter feature accounted for the minute perforations at times. There was usually some narrowing of the lumen due to marked fibrosis that had developed over a considerable time. The majority perforated, sometimes very early, but, as a rule, not until after well-developed fibrosis had taken place. Hemorrhage was rare, and none became cancerous. The regional lymph-nodes were often enlarged and showed inflammatory changes. Microscopic studies showed a necrosis varying in depth from the mucosa to the serosa with round-cell infiltration and fibrosis of varying degrees. Very few showed any change in the vascular system except an occasional thrombosis. The ulcer had not the appearance of those sometimes found in the jejunum in tertiary lues and Levaditi's technic was negative when done. The giant cells of tuberculosis were not seen.

**Etiology**—Zemp<sup>15</sup> believes it can be stated with certainty that the true cause is not known. All of the theories that have been advanced for the development of ulcers in other parts of the gastrointestinal tract have been suggested, as emboli, vascular changes, endocrine disorders, streptococci, irritative action of the intestinal chyme, etc. It certainly is possible that the initial factor may be the result of some previous disease of the

intestinal tract, as the enteric fevers, amebic or bacillary dysentery and cholera. Heterotopic gastric mucosa was present in 1 instance (Puhl's case). A focus of infection from which bacterial



Fig 4—This semidiagrammatic drawing demonstrates the location of the carcinoma in the upper jejunum. Lines *a* and *b* together with the dotted lines demonstrate the amount of jejunum which it was necessary to remove together with its attached mesentery. The shortness of the remaining intraperitoneal jejunal stump as relates to a safe end-to-end anastomosis reveals very well the dilemma encountered. It was readily appreciated from past experiences with high jejunal resections and anastomosis in patients who had developed jejunal ulcers after no loop gastroenterostomy, that no safe anastomosis *in situ* between the ends of remaining jejunum could be accomplished. To meet this situation the plan presented in the following illustrations was undertaken. (Lahey Surg., Gynec. & Obst.)

emboli are carried to the jejunum is possible. Smith's case had thromboangiitis obliterans, but this condition was not evident in the ulcer, and in most

of the cases there were no vascular changes. Trophic disturbances, trauma, and foreign bodies, as a fish bone, are mentioned. Abnormal acidity of the jejunal contents from pyloric dysfunction is inferred. Tuberculosis is possible and should be ruled out by detailed studies. Syphilis is difficult to exclude.

indigestion and abdominal distress from a few weeks to a year or more. Pain was usually present in the midepigastrium or was periumbilical. Sometimes it was general abdominal, in the left upper or lower quadrant, and occasionally in the right or in the back. It was characteristically described as hurt-



Fig 5—In this illustration are shown both ends of the jejunum inverted and safely closed with mattress silk sutures. The parietal peritoneum about the ligament of Treitz and the point where the jejunum becomes retroperitoneal is shown incised about the jejunum so that that structure could be pushed behind the root of the mesenteric vessels into a retroperitoneal position. Following the withdrawal of the finger from the retroperitoneum the remaining slit in the parietal peritoneum was closed by suture. (Lahey: Surg., Gynec & Obst.)

The presence of a possible Wassermann reaction does not mean that the ulcer is luetic. Spirochaetes should be found in the ulcer by Levaditi's method. The majority occurred between the ages of 31 and 60, with from 40 to 60 predominating. They were 3 times more frequent in males than in females.

**Symptoms**—In 7 cases no symptoms were present previous to a sudden rupture, but the remaining patients had had

ing, colicky, cramp-like, or boring. In about 12 per cent, the pain resembled that of duodenal ulcer, occurring  $2\frac{1}{2}$  to 3 hours after meals when the ulcer was very near the duodenum. Food sometimes relieved it and at times aggravated it. Gas, heartburn, sour stomach, belching, nausea, vomiting, and constipation were frequent. In 2 cases bleeding was encountered and in 1 case hiccoughs. As the ulcer progressed with

the development of stenosis, subacute high obstructive symptoms appeared; colicky pains, belching, nausea, vomiting, distention (upper abdominal), constipation, rather marked, and visible peristalsis. Movement of the bowels, particularly after a laxative, usually aggravated the pain and the peristalsis. Acute

were not operated upon at all developed the usual signs of a general peritonitis.

**Diagnosis**—A careful history of chronicity of symptoms should cause suspicion. The subacute obstructive signs of upper jejunal involvement should be easily recognized, as well as the signs of acute perforation. The laboratory stud-

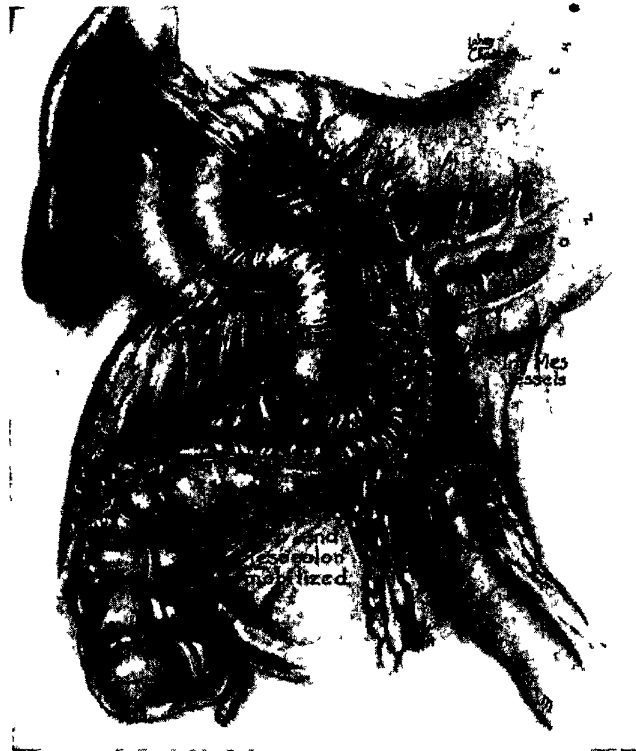


Fig. 6—In this illustration the lateral parietal peritoneum beside the hepatic flexure is shown, incised and the entire hepatic flexure with its attached mesentery so turned down that the retroperitoneal duodenum together with the mobilized and transposed stump of jejunum is at once visualized. With freeing of the retroperitoneal duodenum from its bands of retroperitoneal tissue it will be found to have a sufficiently long mesentery so that it can be carried in front of the transverse colon when that structure is restored to its normal position by putting the hepatic flexure back to the point from which it was mobilized. (Lahey: Surg., Gynec. & Obst.)

perforation occurred in all but 9 cases and was ushered in with a sudden and severe pain in the midabdomen, soon becoming generalized. In several cases the pain radiated to the left side, and in only 1 case did it localize in the right lower quadrant. There was also shock, board-like rigidity, tenderness and usually a diminution of liver dullness. Those in whom operation was delayed or who

ies aid very little, for the gastric analysis is usually low and there is no change in the blood count, except in perforated cases. Fluoroscopic examination frequently gives the diagnosis in the non-perforated cases. Studies of the jejunum 5 hours after the opaque meal often show a regurgitation with stasis and dilatation proximal to the lesion. Occasionally the ulcer may be demonstrated, but more



often narrowing of the lumen is present, due to the stenosis. If the obstruction is complete, a plain roentgenogram will often show the jejunal pattern containing air. In the perforated cases a roentgenogram in the erect position will show an air bubble under the dome of the diaphragm. At operation a thick, ropy, mucoid exudate is usually found.

**Recurrent Peptic Ulcers of Jejunum**—According to Finsterer,<sup>16</sup> recurrent jejunal peptic ulcers are wrongly regarded as surgically incurable. He reports successful results in 19 out of 23 recurrent cases secured by means of *radical resection*. The patients were men between 26 and 56 who had undergone from 2 to 7 abdominal operations



Fig. 7—In this illustration is shown the lower loop of jejunum and the upper loop of transposed jejunum and mobilized retroperitoneal duodenum carried in front of the transverse colon and continuity restored by lateral anastomosis. Note the slit made in the omentum to prevent pressure from that structure on the mesentery of the lower jejunal stump. (Lahey Surg., Gynec. & Obst.)

**Treatment**—Medical treatment is of no value in the majority of cases. As soon as the diagnosis is made of either the perforated or nonperforated cases, operation should be performed. In the *nonperforated* cases, a *resection of the ulcer-bearing area* is preferred. In the *perforated* cases *oversewing* and *drainage* is usually done. Sometimes a *resection with lateral anastomosis* is necessary.

previously. They were predominantly younger men (4 under 30, 5 under 40), 5 of whom had gastric disorders from childhood. Seven of the 8 patients between 50 and 56 had been under treatment from 28 to 39 years. Recurrence of ulceration was due to Y-shaped anastomosis (12), to enteroanastomosis (5) and to insufficient resection (6). Eighteen of the cases showed complete absence of complaints after resection.

One patient had been operated on 7 times within 4 years and had been well after resection for the last 4 years. Several other patients had been restored to health for from 10 to 12 years. The 4 deaths were due, respectively, to necrosis of the gastric wall, cardiac lesions, peritonitis and to a double gastrointestinal fistula. The author believes that failure to employ radical resection when it is indicated accounts in large part for the recurrence of these ulcers. Persistent symptoms after prolonged medical management constitute an indication for resection even in the absence of a gastrocolic fistula or hemorrhages. Finsterer advocates resection of two-thirds of the stomach and more when dilatation is present. He rejects Y-shaped anastomosis except when subtotal resection is carried out to the extent of leaving one-fifth or one-sixth of the normal stomach. He believes that radical resection is indicated in youthful subjects with a history of recurrences. On the basis of more than 3000 cases of stomach resection, Finsterer recommends *local anesthesia* and *splanchnic anesthesia* for protracted operations.

**Jejunal Feeding in Gastrocutaneous Fistulas**—Kjølhed<sup>17</sup> considers feeding through a jejunal sound a valuable method in postoperative gastrocutaneous and duodenocutaneous fistulas. He states that while introduction of the sound is difficult, there is no further discomfort or risk for the patient, and he would first attempt to treat with this method all cases of fistula of the alimentary tract proximal to the jejunum. In the case reported, 51 days passed without any sign of spontaneous healing, but the fistula closed after 9 days of jejunal feeding.

**Congenital High-grade Jejunal Stenosis**—The etiology of these enterodysplasias is still under discussion

and it seems that various factors participate to varying degrees in the origination of these congenital defects. The clinical symptoms are those of ileus; the pulse is small and frequent; and oliguria or complete anuria is present. Usually, the seat of the atresia is suspected but never certain: If vomiting occurs soon after meals and has no fecal odor, high localization is probable; if vomiting occurs some time after meals and has a fecal odor, low localization will be suspected. Survival is always short—rarely more than from 1 to 3 days. From the anatomicopathological point of view, the first mechanism of compensation in stenosis is hypertrophy of the muscular layer which is rapidly followed by progressive dilatation, accompanied by connective-tissue hyperplasia and chronic edema. Ulceration of the mucosa may occur and lead to perforation and peritonitis. Bellini<sup>18</sup> reports the case of a girl, aged 14 months.

*Treatment* must always be *surgical* and differs according to whether the stenosis has not yet resulted in complete obstruction or acute intestinal occlusion is present. In the first form, the surgeon has the time to study the case and to select the manner, time, and method of intervention, while in the second form immediate emptying of the intestine is indicated and resection of the involved part is deferred until the local and general condition of the patient allows the intervention. Consequently, early diagnosis of stenosis means radical intervention to avoid acute ileus or slow cachexia due to progressing stenosis. Careful examination, prompt diagnosis, and immediate medical or surgical treatment are especially important in infants. The intervention must include removal of the stenosed portion and re-establishment of the passage through the intestine. Exclusion of the stenosed part

with laterolateral enteroanastomosis is unsatisfactory because the intestinal content passes into the stenosed tract, where it remains and endangers the general condition of the patient. In unilateral exclusion there also may be reflux of the intestinal content into the involved segment. A step forward seems to be *total exclusion*, provided that a discharge of the intestinal secretion of the isolated segment is furnished through an opening in the abdominal wall. Total exclusion is naturally not a suitable operation for acute ileus, but finds its application in tuberculous stenosis of the cecum in which radical intervention is impossible.

### Ileum

**Primary Simple Ulcer of Ileum**—Tosonotti<sup>18</sup> adds a case of simple primary ulcer of the small bowel to 75 reported in the literature. These were found for the most part in the ileum and were classified as acute or chronic. The former type was described for the first time in 1833 by Leotta as a cleanly demarcated area of necrosis in which signs of inflammation were absent or minimal, consisting at most of a slight margin of infiltration. The chronic type, on the other hand, was characterized by extensive induration involving the margins and base of the lesion, as well as contiguous portions of the bowel wall, and frequently causing adhesions with approximated loops of gut. The *jejunal ulcer* presents a syndrome which is predominantly dyspeptic, characterized by anorexia, acid eructations, occasional vomiting, and pain, which usually comes on some time after eating and may be burning or cramp-like; this pain is referred to the epigastrium and left upper quadrant and is brought out by deep palpation and alleviated by alkalis. Hematemesis and melena may be present. These features, with negative Roentgen

examination of the stomach and duodenum, should direct suspicion toward the jejunum. In the *ileum*, on the other hand, the simple ulcer is manifested by sudden crises of colic localizing in the lower abdomen in the left or right quadrant, diarrhea, and possible melena. Here, too, the pain is periodic and interspersed with periods of remission. It is plain that in the latter case differentiation will be difficult from perforations of an acute appendix or a Meckel's diverticulum.

The *etiology* and *pathogenesis* of this lesion, as of the peptic ulcer, are controversial. The author believes that the cause is primarily vascular, and as basis for his conviction points out that the small vessels which supply the intestine are essentially end-arteries and their occlusion would result in infarct formation. Further, the round form, somewhat coned out, with clean margins as if punched out in normal mucosa, and the sudden onset without a history of intestinal disturbances offer further evidence of a vascular etiology. It is further hypothesized that toxins such as alcohol and nicotine, which are excreted through the gastrointestinal tract, may play a secondary rôle in the development of such ulcers. The interesting suggestion has been made in this connection, as in the case of ulcers occurring in Meckel's diverticula, that they are due to ectopic islands of gastric mucosa. There are many reports, however, in which histological examination has failed to reveal such evidence.

The *treatment* for this entity is strictly *surgical*, because of the marked tendency toward ulceration which characterizes the lesion.

**Regional Ileitis**—The presence of nonspecific, tumor-like, chronic inflammatory masses in the bowel has been recognized and reported throughout the

years; but it was not until 1932, when Crohn, an internist at Mt. Sinai Hospital, New York City, reported 14 cases, that the subject was thoroughly studied and investigated. Crohn's cases are represented by 13 operative, resected specimens, each characterized by a necrotizing and sclerosing process, occurring in the

granulomas, or tumor-like inflammatory masses, includes such lesions as occur about a diverticulitis of the sigmoid, a slowly penetrating gastric ulcer, the so-called fibroblastic appendicitis, and the specific granulomas of tuberculosis, syphilis, actinomycosis, and Hodgkin's disease.

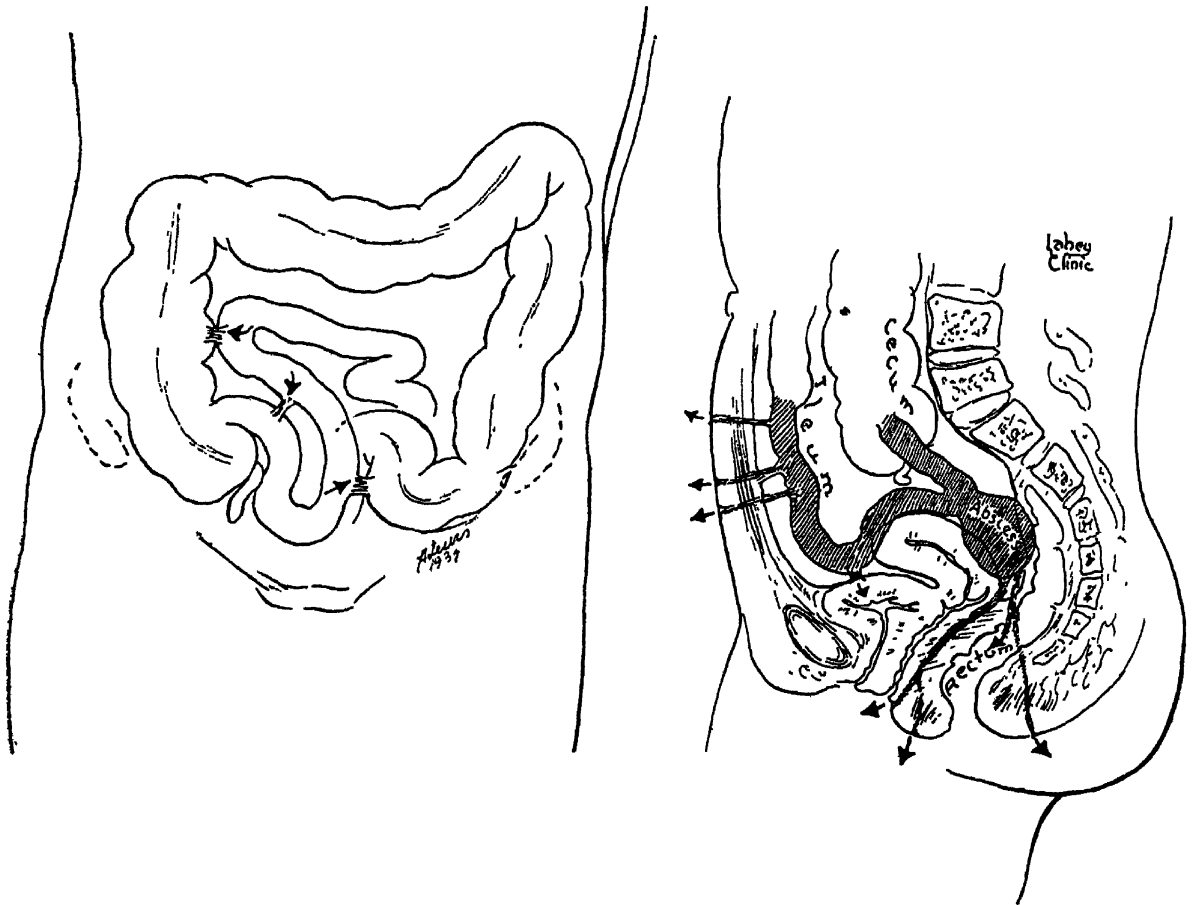


Fig. 8—Types of fistulas encountered at operation. The diagram on the left shows the fistulous tracts formed between the lesion and an adjacent loop of small bowel, the terminal ileum, the ascending colon and the sigmoid. That on the right illustrates the fistulous tracts noted extending through the abdominal wall (the commonest type) and into the bladder and types of perirectal fistulas. (Marshall: New England J. Med.)

terminal ileum and ending abruptly at the ileocecal valve. These cases were similar enough in nature and different enough from the many other miscellaneous chronic inflammatory lesions of the bowel to warrant segregation as a group. Crohn called this clinical and pathological entity "regional ileitis." The other great heterogeneous group of infective

The literature is replete with isolated cases of nonspecific, inflammatory masses occurring throughout the gastrointestinal tract, frequently mistaken for carcinoma or tuberculosis. Crohn's cases, however, were so thoroughly observed, studied, and reported, that subsequent reports seem to justify his isolation of this particular condition. His original conception

stands unchanged. Nothing has been changed, but much has been added. Later, it was observed by Crohn and others that the disease, though usually involving the terminal ileum, could occur in other parts of the bowel. This fact gave rise to different terms to include the entire concept of the disease, *i. e.*, "regional enteritis," "chronic cicatrizing enteritis," "localized hypertrophic colitis," etc. Also, the lesions were sometimes found in 2 or more areas at the same time, with normal bowel lying between the areas involved.

The disease is characterized by its peculiar necrotizing and sclerosing inflammatory process, by its predilection for the terminal ileum, and by its remarkable tendency to slow, gradual perforation, with the formation of small, intra-abdominal abscesses and fistulas. These fistulas may occur between loops of bowel, or between bowel and bladder, or bowel and the surface of the body.

The disease tends to occur in young adults, but may occur in individuals of any age. In its early stage it may simulate acute appendicitis so closely that appendectomy is frequently done. Finally, progression of the disease frequently leads to stenosis of the lumen of the bowel with resulting obstructive symptoms.

**Etiology**—The etiology of the disease is unknown; Pumphrey at the Mayo Clinic has made an intensive bacteriological study without finding any specific causative organism. All possible tests for tuberculosis are negative. Agglutination tests fail to reveal any specific reaction. The similarity to lymphogranuloma inguinale suggests a virus infection. The Frei test, however, is negative. Stained sections fail to reveal any special organism. The condition has been fairly well reproduced by injecting a sclerosing solution into the mesenteric

lymphatics and those of the subserosa. The disease suggests an infective process, but nothing definite has been proved.

**Pathology**—Regional ileitis is a slowly creeping pathological process so indistinct at its periphery that its real extent cannot be identified by the sense of touch or the naked eye. It is characterized by an ulcerating process in the mucosa and by a hyperplastic process in the wall of the bowel. In the early phases, as studied at operation, there is an exudative type of inflammation which gives rise to a soft, thick, edematous bowel wall with a reddish, dull serosa which has lost its gloss and luster. The mesenteric nodes are soft, hyperplastic, and enlarged. The disturbance may subside, or progress to a chronic stenotic phase with acute exacerbations. Small ulcerations occur in the mucosa, giving rise to irritative symptoms. Within the submucosa and the muscularis layers of the bowel are found areas of exudative and hyperplastic inflammation, which with gradual progression, finally yield a thick, stiff, fibroblastic type of wall, compared at times to a worn-out rubber hose. As a result, scar tissue is built up which encroaches upon the lumen, producing stenosis. Microscopic section shows a nonspecific, chronic inflammatory process. The disease may spread, usually by extension from the periphery. Sometimes, even with radical resection to include what appears to be normal tissue, there is reappearance of the lesion, though this is not common.

Why or how recurrence or extension takes place is not known. This quality of the disease certainly differentiates it from other granulomas of the bowel. In Crohn's first description of regional ileitis it was thought that the granulomatous lesion of the bowel remained confined to the terminal ileum, ending sharply at the ileocecal valve. Since then,

however, it has been found that the condition may involve not only the terminal ileum but any part of the ileum and even the jejunum or colon. One of the characteristic findings in the disease is that the affected bowel may not be involved in a continuous inflammatory process, but that normal segments of the bowel may intervene between the diseased portions. Failure to recognize this fact and to look for evidence of a more extensive process may account for the failures or recurrences reported following resection. The colon itself does not remain free of the disease, and frequently on abdominal exploration the latter is found to involve the cecum and ascending colon as well. In a series of 29 operated cases, frequently the cecum, ascending colon and, in 1 case, the jejunum were found to be affected.

Involvement of the ileocecal junction is quite a common occurrence, and was noted in 16 of the 29 patients observed by Marshall.<sup>20</sup> In 3 other cases the lesion had extended into the cecum and had produced thickening of the wall with ulceration. In 10 cases the terminal ileum alone was involved, while in 2 the disease appeared to be confined to the upper loops of jejunum or ileum. In 2 other cases most of the ileum and at least a portion of the jejunum were involved. In such a case coming to autopsy without operation, almost the entire small intestine consisted of a continuous cicatrizing, granulomatous, inflammatory mass. In still another patient under observation, roentgenological examination revealed that almost the entire small bowel was involved. In the majority of cases, however, the process affects the terminal ileum, involving the last 7 to 35 cm.

**Roentgenologic Manifestations** — X-ray studies of this condition are invaluable for the correct diagnosis and

appreciation of regional ileitis. Crohn's article has made the internist and surgeon aware of the importance of x-ray studies of the small intestine as well as stomach and colon in any vague abdominal complaint. Kantor, radiologist at Mt. Sinai Hospital, called attention to a constant filling defect in the affected segment of bowel, usually in the terminal loop of the ileum, and also to the so-called "string sign," a thin, irregular, linear shadow suggesting a cotton string, caused by encroachment of the pathological process on the lumen of the intestine. This sign is not pathognomonic, but such a picture is apt to denote regional ileitis. Just as the clinical picture varies with the pathology, so will the roentgenological picture. The usual pathological combination is that of hyperplasia and ulceration, with the former predominating. With the hyperplastic phase dominant, the x-ray film will represent excess fibroblastic, scar-tissue formation, which results in narrowing of the lumen, shortening of the affected segment and loss of normal pliability and motility of the bowel wall. If the ulcerative features predominate, the mucosal relief of the segment will be abnormal. The usual picture represents the combined process. The x-rays remain the most important single diagnostic agent.

**Clinical Course**—Crohn divided the clinical course into 4 stages, which vary according to the pathology: (1) An acute intra-abdominal disease with peritoneal irritation to give right lower quadrant pain and tenderness, fever, and leukocytosis. This, of course, resembles the picture of appendicitis, and well explains the frequent recourse to appendectomy. (2) Symptoms of enteritis due to ulceration of the mucosa. Here there is usually cramp-like pain, diarrhea, occasionally with mucus and blood, bouts

of fever, and loss of weight. (3) Symptoms of chronic obstruction due to stenosis. This stage gives colicky pain with distention, nausea, and vomiting. (4) Symptoms due to slow perforation with formation of abscesses and fistulas.

If this condition is kept in mind, the diagnosis often can be made clinically, or at least suspected. As stated, this disease usually occurs in young adults. The early phase closely simulates acute appendicitis; however, the presence of diarrhea in an adult and the possible suggestion of a mass in the right iliac fossa may put one on the alert against the diagnosis of acute appendicitis. Dixon,<sup>21</sup> of the Mayo Clinic, listed the following symptoms in a series of 44 cases: (1) Loss of weight, 43 (average of 21 pounds); (2) diarrhea (3 to 6 times), 30; (3) palpable mass, 32; (4) fever, 28; (5) obstruction, 28; (6) abdominal cramps, 25; (7) anemia, 18; (8) nausea and vomiting, 18; (9) pain other than cramps, 12; (10) blood in stools, 7; (11) fecal fistula, 9; (12) appendectomy, 24. In a series of 50 cases the following symptoms were listed by Jellen: (1) Abdominal pain, 36; (2) loss of weight, 30; (3) palpable mass, 29; (4) diarrhea, 26; (5) anemia, 21; (6) fever, 19; (7) fistula, 18; (8) vomiting, 14.

In 110 of Crohn's cases, 11 had internal fistulas, 12 external, and 20 perianal, perirectal, and rectovaginal fistulas. The dominant features to be kept in mind in making the diagnosis are a history of a previous appendectomy, abdominal pain or cramps, bouts of mild diarrhea, loss of weight, and a low-grade fever. Examination usually reveals a mass in the right lower quadrant, the scar of a previous appendectomy, evidence of a fistula, emaciation, and anemia.

**Differential Diagnosis**—(1) *Tuberculosis*—This also may produce an ulcerative and hyperplastic process in the bowel, especially in the ileocecal area. It is impossible at times to differentiate between the 2 with certainty preoperatively or at operation. A chest plate should always be taken, for an intestinal lesion with a positive pulmonary lesion is likely to be tuberculosis. Primary intestinal tuberculosis is rare.

(2) *Chronic Ulcerative Colitis*—Here the pathology predominates in the rectum and left colon. Sigmoidoscopic examination usually is negative in regional ileitis, and positive in ulcerative colitis. The diarrhea, fever, blood, and mucus in the stools are more marked in colitis, and usually there is tenesmus.

(3) *Malignancy*—Malignant lesions can be differentiated easily by x-rays. Cancer also is rare in the small bowel. The clinical course also varies.

(4) *Syphilis*—Syphilis of the small bowel is rare. A Wassermann test always should be done. The stool should be examined for ova, parasites, amebae, blood, and pus.

(5) *Bacillary Dysentery*—This is eliminated by a negative agglutination test. A negative Frei test rules out lymphogranuloma inguinale. If a fistula is present, the pus should be examined for actinomycosis and tubercle bacilli.

**Treatment**—Experience up to the present definitely tends toward surgery. In the early exudative stage of the disease, however, the treatment is symptomatic. Should early regional ileitis be discovered during operation for a condition diagnosed preoperatively as acute appendicitis, the affected ileum should not be disturbed. If the appendix is normal, and it usually is, it also should not be disturbed. Appendectomy at this time is frequently followed by the formation of a fistula. These acute early cases merit

a careful follow-up; some of them progress to a chronic stage, and such progression should indicate early operation, which in turn makes for a lower mortality. Obviously, later stages of obstruction, fistulas, and abscesses require surgical relief. Two choices are available, *i. e.*, (1) *an ileo-transverse colostomy*, with or without transection of the ileum without disturbing the affected segment; (2) *resection of the diseased area and anastomosis*. For several reasons, some surgeons lean toward the former method.

Even where *resection* is contemplated, a 2-stage procedure is safer and has a lower mortality. A fair number of cases will quiet down and not need further surgery. (Crohn states that about 50 per cent will do well. The figures of the Mayo group coincide.) *A preliminary ileo-transverse colostomy* allows the patient to put on weight; allows for closure of fistulas; permits the edema and inflammation about the segment to subside. Should this procedure be done, the ideal method seems to include transection of the ileum, to give the diseased bowel a complete rest; however, this desire must be modified by the possible danger of obstruction in the affected area distal to the transection, which may cause a blow-out of the blind stump. In spite of the fact that a plain, side-tracking anastomosis is attended with a smaller mortality (only slightly smaller, to be sure), and in spite of the fact that about 50 per cent may obtain relief, most surgeons believe resection should be done, either in 1 or 2 stages.

The outcome of a *simple anastomosis* in the individual cases cannot be predicted; some are benefited; in others the process may spread, or fistulas may occur, or slow perforation with abscess formation, or obstruction may ensue.

These complications may make resection a necessity at a later date, with a higher risk. When *resection* is done, ample bowel must be removed; the possibility of multiple areas of involvement always should be kept in mind. Koster, in 126 collected cases with resection, reported a 15 per cent recurrence; Crohn, a 7.7 per cent recurrence; the remainder of his patients were completely cured.

Although surgery remains the treatment of choice in all but the early acute cases, and resection the favored method when surgery is decided upon, other factors must affect the surgeon's judgment, such as the age and general condition of the patient, the location and extent of pathology, and the presence or absence of other complications. These latter factors may make medical treatment the safer procedure. The chronic, progressive, nontreated case of regional ileitis has a gloomy outlook. It runs a long, downhill course, with debility, malnutrition, diarrhea, and anemia. Multiple fistulas and foci of sepsis may form, or obstruction may occur. Crohn stated that he had never seen spontaneous and complete resolution in a case of chronic regional ileitis.

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## CECUM

### Invagination of Haustra of Cecum

**Etiology**—The predisposing factor is a mobile cecum; the immediate exciting factor may be ulcers, tumor, foreign body, spasm, or inflammation. Accumulation of oxyuris in the cecum was the cause in Kyiovsky's cases. In the 2 cases observed by Soven<sup>22</sup> the occurrence of trichocephali, which caused ulceration in the cecum and even burrowing into the cecal wall, were the immediate cause of the invagination.

**Symptoms**—The symptoms pointing to invagination would be the sudden oc-



currence of signs of obstruction, the absence of fever, and the early presence of a painful cylindrical swelling in the right iliac fossa. Unfortunately, the signs are vague. There may be epigastric pains with localization in the right lower quadrant, as in acute appendicitis. Anatomically, it consists of a lateral invagination of 1 of the first 3 segments of the cecum between the anterior and the posterolateral longitudinal bands. Partial invagination of the appendix may accompany that of the first cecal segment. The invaginated part undergoes circulatory disturbances and may become gangrenous.

**Treatment**—This is surgical. The invaginated segment may be easily reduced. A *cecopexy* may be done. If there is a tendency to recurrence or if the bowel is gangrenous, a *right hemicolectomy* with a *lateral anastomosis* of the ileum to the transverse colon may be done.

### POSTOPERATIVE INTES- TINAL PARALYSIS

**Treatment**—A comparatively simple and yet highly effective procedure employed by Stahnke in Ludwigshafen, also described by Genkin and Miljawska was employed by Suren<sup>27</sup> in several hundred cases of postoperative ileus. Two tablespoonfuls of *sodium chloride* are dissolved in 5 ounces (150 cc.) of lukewarm water and introduced as a drop *enema* high into the rectum. The enema may be effective before it has been completed, frequently after 5 and always within 15 minutes. The sodium chloride enema, however, remains ineffective when a mechanical obstruction exists. In such cases the enema is repeated after an hour and, if ineffective, surgical treatment is decided on. Thus,

the sodium chloride enema is also of value in the differential diagnosis.

### ILEUS

**Acute Mechanical Obstruction of Small Bowel**—McKittrick and Saris<sup>28</sup> studied 136 cases. From 70 to 80 per cent of these patients had a previous laparotomy. Six per cent had been operated on for a previous obstruction. Eight patients were not operated on because of spontaneous recovery. Twenty-seven patients died, and 4 were not operated on in this group. The hospital mortality was 20 per cent. Of the group of 124 patients operated on, 23 died, giving a surgical mortality of 18 per cent. Strangulation is the most important single factor in determining the outcome of a case of acute obstruction of the small bowel. It was present in 33 per cent of the total group and was the cause of death in more than one-half of the fatal cases.

**Symptoms**—Severe, sudden, colicky abdominal pain usually followed by vomiting, cessation of bowel movement and passage of flatus, high-pitched peristalsis audible over the abdomen. The temperature was normal or subnormal unless gangrene and perforation had resulted. A "scout" film of the abdomen should make possible a definite diagnosis of early obstruction of the small bowel in a high percentage of cases. Acute obstruction of the small bowel usually occurs at a single point and is caused by a band or adhesions from a previous operation. Eighty-one per cent of the 136 cases had a single point obstruction.

**Treatment — Operation** should be performed within 24 hours. After 24 hours, other factors, such as distention, dehydration and chemical imbalance rapidly assume importance. *Simple drainage* of the strangulated loop of dis-

tended bowel without exploration or resection will further lower the operative mortality in many instances.

#### Acute Intestinal Obstruction<sup>29</sup>—

Acute intestinal obstruction is not a single clinical entity, but is actually a collection of conditions with certain common factors, the most obvious of which are the inability of the gut to propel its content untrammelled throughout its entire length, and the development of distention of the intestine. Variations in etiologic factors, such as the site of obstruction, integrity of blood supply, general condition of the patient before onset, and the length of time elapsed between onset and beginning of treatment, influence the mortality rate regardless of the effects of operative treatment.

*Etiologic factors* in the initiation of mechanical obstruction of the bowel have long been well understood. Approximately one-half of all the cases of intestinal obstruction are caused by protrusion of the intestine through external hernial orifices. This has been well borne out by many published statistics. Inguinal and femoral *hernias* are the commonest offenders in this regard. The mortality associated with obstruction due to hernia is low as compared to that of most other causes, even though the incidence of strangulation is likely to be high. The obvious reason for this lower mortality is that the diagnosis is made early and a standard procedure, early operation, is not usually unduly delayed. In addition, the operation is likely to be simpler, since the lesion is not difficult to find.

Next to external hernia, the commonest etiologic factor is *adhesions* and of these, adhesions resulting from previous surgical procedures form the largest group in this category. These 2 conditions, external hernia and adhesions, account for approximately three-fourths of all cases of acute intestinal obstruction.

Wolff<sup>30</sup> has called attention to the fact that *volvulus* may occur in children and lead to violent, repeated crises, and then disappear again. Havens<sup>31</sup> reported a case of intestinal obstruction caused by *colloidal aluminum hydroxide*. The preparation used (amphojel) contains about 5 per cent aluminum hydroxide, which, combined with the astringent effect produced, may favor constipation, especially when there is blood in the intestine.

Obstructions which are likely to be associated with interference with the mesenteric blood supply are, as a rule, more serious in nature, since in addition to the possibility of necrosis and perforation of the intestine, there is a greater tendency to early toxemia and shock. The high mortality in most published series is no intimation that decided effort has not been made to understand the cause of death in acute intestinal obstruction. A considerable amount of clinical and laboratory investigation has been expended upon this problem.

Three main theses have been advanced to explain the cause of death in this condition. The oldest theory concerning the cause of death in intestinal obstruction is that a potent toxin is formed. The possibilities for the production of this toxic material are (1) that the bacteria, particularly Welch bacilli, elaborate a specific toxin and that specific antitoxins are effective in protecting against this toxin (this viewpoint is contested by Owings and McIntosh and Oughterson and Powers, who could find no protective action of *B. welchii* antitoxin in experimental animals); (2) that the toxin results from an abnormal mucosa or secretions into the gut; (3) that the toxin arises as the result of bacterial growth in the obstructed gut and is not specific; (4) that the toxin is formed from putrefaction of intestinal content; and (5) the symptoms of toxemia actu-

ally are the results of bacteria migrating from the obstructed loop, causing a bacteriemia, as suggested by Borszeky and Genersich in 1902. This latter view was promptly and effectively refuted by Clairmont and Ranzi. The nature of the toxic substance is likewise a much debated subject as is also the mode of its transmission from the intestine.

The concept that in simple obstruction death results from loss of fluids and salt has received considerable consideration, since it was shown by Hartwell and Hoguet and McLean and Andries that animals with obstructed loops of bowel survived longer if a saline solution was administered. That the problem of fluid and salt loss is important in these cases has been referred to by Hayden and Orr, Gamble and McIver, White and Fender and many others. That it is the sole cause of death is doubtful, since while survival time is increased by the administration of salt solution, death nevertheless occurs. In those cases in which strangulation is a factor, death occurs early even in animals well hydrated.

The fact that late in the disease patients with acute intestinal obstruction appear similar to patients in shock, has suggested that there is some relationship between these conditions.

The concept suggested by Braun and Boruttau in 1908 and occasionally referred to by others that the element of shock was quite important in explaining the cause of death in intestinal obstruction, has recently received some attention in German literature. An additional article by Braun in 1925 reiterated the concept that associated with occlusion there is strong nervous stimulation which is increased by the addition of physical and chemical stimulation from the altered intestinal content. These stimuli are supposedly mediated not only through reflexes of nerves in the intestine and asso-

ciated autonomic ganglia, but also act centrally. There results a true picture of shock, with associated fluid loss, blood concentration, and capillary stasis.

Gudladt, who accepts this concept, has, as recently as 1939, reported on pathologic findings in 190 cases of intestinal obstruction. He believes that his findings support the view that the cause of death is associated with damage to the circulation. He also, however, reports changes in the lungs which appear to support the concept of Becher that the lung plays an important rôle in detoxifying substances absorbed from the intestine. Scudder, Zwemer, and Whipple reported results on studies of the potassium content of blood in intestinal obstruction, and point out that acute intestinal obstruction and adrenal insufficiency have many features in common.

Scudder, Zwemer, and Truszkowski reported an elevation in the level of potassium in the blood of cats following obstruction, and suggest that a high potassium level might be the cause of death. This has likewise been reported by Cutler and Pijoan in the dog. In the study of human cases, however, Falconer, Osterberg and Barga did not substantiate these findings. In fact, they noted a fall in the potassium content in the serum and suggest, as did also Scudder, Zwemer, and Whipple, that potassium is actually lost through secretions from the upper intestinal tract.

Within recent years there has been a renewal of interest in the part that distention plays in the cause of death from intestinal obstruction. As an important finding in late cases of intestinal obstruction, distention is stressed as a predominating feature in diagnosis. The rôle that distention plays in the train of events which leads to a fatal outcome in these cases, while referred to by most authors, has not received attention commensurate

with its importance until the last decade. Burget, Martzloff, Thornton, and Sukow, Herrin and Meek, and Taylor, Weld, and Harrison stressed the importance of distention *per se*, with regard to the initiation of symptoms and to the recovery of animals with experimentally produced obstruction. Burget and his coworkers showed that if a closed loop obstruction was kept decompressed, no symptoms of obstruction resulted.

Herrin and Meek and Taylor, Weld, and Harrison presented experimental data to support the close relationship between the course of events in obstruction and the distention, and indicated that it was possible to cause the entire picture shown by animals with obstructed loops, when no obstruction was present, provided distention of the gut was produced.

**Treatment** — Wangensteen and his associates have done much to focus attention upon the rôle of distention as a factor of great importance in acute intestinal obstruction. The initiation of the use of *suction drainage* in the treatment of acute intestinal obstruction, while popularized by these workers, has been sporadically suggested for many years. Suction drainage by use of gastric or duodenal tubes is but 1 method for accomplishing relief of distention of the small bowel. Unfortunately, the method rather than the principle has been regarded as fundamentally important, and it is found that many condemn or praise the method without consideration of the basic principles involved. Reiterating these principles, Wangensteen has reported mortality statistics of cases treated by suction drainage which attest to the efficacy of the method but it is to be noted that the cases so treated were a group, most of whom were suitable for this type of treatment, and other cases

were submitted to various operative procedures.

In 1938, Abbott and Johnston reported the use of *intestinal intubation* in the treatment of simple intestinal obstruction by the use of a tube developed by Miller and Abbott. The rationale of its use was based on the proposition that the distended intestine could be decompressed better with suction applied directly above the point of obstruction than at higher levels. This, in effect, is tantamount to an enterostomy without the necessity of an operative procedure. In addition to drainage from a vantage point, it permits the feeding of the patient. Further studies with this method have indicated its usefulness, not only with regard to the treatment of intestinal obstruction, but also for localization of the obstructing lesion and for the preparation of the patient for operation.

Sufficient experience has been gained with the use of intestinal intubation in the treatment of simple intestinal obstruction and adynamic ileus to illustrate its efficacy. In several clinics where it has been used extensively, but judiciously (Hospital of the University of Pennsylvania, Detroit Receiving Hospital, and Presbyterian Hospital in New York), there has resulted a marked reduction of the mortality rate from acute intestinal obstruction. For the past 2½ years the mortality from small intestinal obstruction at the Detroit Receiving Hospital, including all cases of intestinal obstruction whether the obstruction contributed to the death or not (except those due to strangulated external hernia), has been approximately 23.9 per cent. The mortality from simple acute obstruction treated by intubation was 9 per cent. Similar good results have been attained at the Presbyterian Hospital.

The limitations of the method and difficulties of its use, as well as its

advantages, are set forth in publications of Abbott and his associates and Johnston and his colleagues. It is not possible at present to obtain an adequate appraisal of the effect which the judicious use of suction drainage has had on the mortality from small bowel obstruction. It is much too early, since its place in therapy was enunciated by Wangensteen and since the introduction of drainage from the lower reaches of the bowel, to allow for large series to have been reported.

It is to be recognized as significant that in comparison to older statistics, those presented by Wangensteen and associates have a decidedly lower mortality, and the writer has been able to bring about a further decrease in the mortality of his own cases. It is worthy of note that Wangensteen has surveyed all types of cases of small bowel obstruction and reports a mortality of 17.9 per cent, reducing the mortality from obstructions within the abdomen to below that commonly attained in those cases associated with external hernia. The cases reported by Wangensteen were not a personal series but were cared for by several individuals. This group of surgeons, however, must recognize the place of suction drainage in the broad problem of the therapy of intestinal obstruction, based on an understanding of the pathology and physiology involved.

The problem of treatment of this condition must be based on principles involved without regard to strict adherence to any method. The well-known saying that "the sun should never set on an unoperated case of intestinal obstruction" is as erroneous and as productive of poor results as such general dicta are likely to be, if followed strictly. Wangensteen has pointed out that there is a mortality of treatment as well as of disease, a fact which too often is ignored.

Treatment carried out on the basis of dicta, or fixed routine, without regard to the pathologic lesion and physiologic principles involved, and without the consideration of obstruction of the bowel as a diversified problem, must lead to many unnecessary fatalities.

An additional method of decompressing the distended intestine has been suggested by Rosenfeld and Fine, who found that in cats it was possible to cause a marked decrease in intraluminal pressure produced by distention of air or nitrogen if the animals were made to *breathe pure oxygen*. This procedure offers promise for use in intestinal obstruction, even though it is likely to be slow in its action in decreasing the amount of gas present, because of the salutary effects offered in more effective oxygenation in a patient whose respiratory activity is hampered by distention.

Regardless of the possibilities for the reduction in mortality from intestinal obstruction by careful consideration and use of suitable methods of treatment, it is not likely that the mortality from this condition will be lowered materially until the importance of early diagnosis is universally recognized. Within a few hours after the onset of obstruction, when distention is likely to be slight, operation is attended by low mortality. When distention is marked, dehydration present, and changes in blood chlorides and urea are marked, the difficulties of treatment are greatly increased.

It is well to point out that in addition to the recognition of the early symptoms of intestinal obstruction, the *Roentgen rays* offer early *diagnostic aid*. The use of contrast media is not necessary, and is actually contraindicated early in the disease. In fact, Roentgen rays without contrast media offer the only early laboratory finding of any advantage and should be utilized in all suspected cases.

While the upright film may reveal fluid levels and indicate the presence of obstruction, the supine film will in many instances indicate the level of the obstruction.

When the diagnosis of obstruction is established early, before marked distention and dehydration are present, operation should not be delayed. *Early diagnosis and treatment*, so important in simple acute obstruction, becomes imperative in those cases where there is interference with the mesenteric blood supply, not only because of the possibility of releasing the occlusion to the vessel early, thereby preventing necrosis of the bowel, but for the prevention of the development of the severe toxemia which is so rapidly fatal. The early differentiation between simple and strangulated obstruction is not easy. The diagnosis of strangulation is based on the severity of the onset, the rapidity of progression of symptoms, evidence of a localized gas-filled loop, and symptoms out of proportion to the amount of distention present. Increasing pulse rate, falling blood-pressure, and presence of localized tenderness are likely to be found late and should always suggest strangulation.

Gatch has suggested that it is possible to treat such patients without operation until the strangulated loop becomes well walled off, as is practiced in cases of appendiceal abscess, but it has not been considered wise to defer operation in cases of suspected strangulation. Preparation by *blood transfusion, intravenous saline solutions*, and the *insertion of a tube* at least into the stomach, need not delay *operation* long and are important aids. Consideration of the importance of distention as the initiating factor in the sequence of events following simple acute obstruction of the bowel does not imply any particular form of therapy.

*Relief* of distention can be brought about by *operation* or by removal of the distending content from within the bowel by means of *intubation*. Which of these methods is to be used depends upon the problems presented by the patient and not by custom. There undoubtedly have been instances where an attempt has been made to apply *suction drainage* for treatment of intestinal obstruction without regard to the problem presented by the patient and it is to be expected that such attempts will be disheartening. The concept that suction drainage is a specific regimen for intestinal obstruction is but little less dangerous than the concept that early operation is indicated in all forms of intestinal obstruction. It is only by early diagnosis, a consideration of the underlying principles involved, the conscientious appraisal of the patient, and the utilization of the best available forms of treatment that the unnecessarily high mortality from intestinal obstruction will be effectively lowered.

### Ileostomy and Colostomy

**Management of Ileostomy**—Today, competent drainage of the upper gastrointestinal tract can be obtained by means of continuous duodenal suction, and by means of the Miller-Abbot tube. Occasionally, however, ileostomy is done for *intestinal obstruction* and as a means of taking pressure from the point of anastomosis where the small intestine has been resected. Accidental type of ileostomy may result because of difficult technical conditions in carrying out an operative procedure, or may result because of infection eroding an opening into the small intestine. In the Lahey Clinic<sup>32</sup> protection to the abdominal wall in these accidental openings is accomplished by *continuous suction* and by placing materials that may be partially imper-

vious to the intestinal contents, such as *copper bronze powder* or *aluminum powder*. *Kaolin* and *Fuller's earth* are also used as drying powders.

Years ago a *button closure* was employed. An ordinary button is used that is a little larger than the opening in the intestine. This button preferably should have but 2 holes in it. It is then turned upside down, with the concavity upward, and a linen thread put through the 2 holes, and that is inserted into the opening. A second button of even larger size can then be tied down to the smaller button, which remains within the intestinal lumen, and it may be possible by this means not only to prevent a large loss of fluid and salts, but to get healing of the enclosed abdominal wall. In order to get rid of it, it is not as difficult as might be surmised, because all that has to be done is to cut the thread; the inner button passes down along the intestinal tract and the outer button of course delivers through the wound. This button closure may prove useful, and Cattell suggests its employment in this type of accidental intestinal opening. The next thing is the *operative closure with actual resection of the fistula* and some type of *anastomosis*.

In a third group of patients, an ileostomy may be required when there is a complicated situation in the colon and it will be difficult to do a resection and anastomosis. An ileostomy may be essential in *chronic ulcerative colitis*. It is used in this instance to put the large intestine entirely at rest, in order to permit as satisfactory healing as possible of the ulcerated condition in the colon. As soon as the operation is completed, the entire abdominal wall in the region of the ileostomy is painted with *tincture of benzoin*. This produces after several applications quite a tough membrane which will protect it from ileal discharge.

The discharge is kept from the abdominal wall by a catheter. The catheter is removed in 2 or 3 days and a suction apparatus applied for 4 or 5 days. Following this, the abdominal wall can be protected with the powders before mentioned.

When the patient is ready to get out of bed, an ileostomy apparatus is applied and if the ileum projects sufficiently far above the skin, this will discharge directly into the bag. When an ileostomy is performed it may be permanent, with a remission of the disease and nothing further necessary; it may be temporary with good healing of the colon; or it may be a first stage of a necessary complete colectomy. These patients, after a considerable interval following removal of the colon, have the function of the colon taken over by the ileostomy. The stools become less irritating and less liquid. The best, however, that can be obtained with ileostomy is to expect 5 semi-formed stools a day. By the use of a certain type of ileostomy apparatus, the patient's day can be started with 3 small rubber containers in the bag. By mid-morning the inner bag can be removed and discarded, and then the other 2 used. Again, about 2 hours after the midday meal, when the movements have been most marked, that bag can again be discarded, and it can be done again in the evening. That means that the activity of individuals with ileostomy need not be limited and they can pursue a reasonable degree of activity in spite of its presence.

**Management of Colostomy** — This may be *temporary* for the relief of an obstructing diverticulitis or for an inoperable carcinoma of the sigmoid or rectum. It is *permanent* in those cases in which it is necessary to resect the rectosigmoid and rectum for carcinoma in this site. It is important to have some

bowel projecting sufficiently far above the skin. Suturing the skin to the rectus fascia eliminates the fatty layer. The patient is taught to control his diet. This is done by giving a low residue, constipating diet, and each patient is given a *diet* with 3 different divisions. The first is to be followed for 1 or 2 months until satisfactory control is obtained. The second adds a considerable freedom to the diet and finally but 4 or 5 articles of diet are restricted. Beginning about the eighth or tenth day after operation, after the resection, where colostomy has been performed, an irrigation in the form of an enema is given, and this is repeated every second day. By this means the colon can be emptied successfully and it requires about 48 hours to have the colon fill again, so that there will be no spilling over. This 2-day irrigation schedule, so-called, is pursued for a period of about 2 months. Following this, the patient is placed on a 3-day irrigation schedule. It is very interesting to talk with individuals on whom this 2-day and 3-day irrigation schedule has been used, because their immediate thought is: "If my bowels don't move every day I am sure that I cannot continue in normal health." To begin with, the resistance of the patient in this regard must be overcome. A moderate degree of constipation is anticipated and desirable. It must not become too great, however, because if it does so, there will be difficulty in the irrigations. Likewise, if the colostomy has not been performed satisfactorily and if a narrowing occurs, such as a stricture or beginning stricture, there will be trouble with the irrigations. A third factor in control has to do with regularity. Just as the bowel habit should be a regular thing, it remains so with colostomy present. If the same period of time is taken, that is in the evening of the second or third day, and

an irrigation taken at that time regularly, there will be little difficulty in controlling a satisfactory movement.

Patients have been known to go for a period of years without difficulty. Patients with colostomy are subject to the same disorders as other individuals, however, and may also develop a diarrhea under certain conditions. They are instructed, therefore, to take a *constipating diet* at this time, with a teaspoonful of *paregoric* every 4 hours and 2 or 3 glassfuls of *boiled milk* a day. This will be sufficient to overcome any period of diarrhea in a very short period of hours. These individuals wear no type of colostomy apparatus.

Every patient who has a colostomy becomes an inventor at once, so they have different types of domes and different types of belts and different ways of attaching small pads to the abdomen. A French catheter of size 22, an ordinary enema bag, and a shut-off valve, and that is all that is required to take an irrigation, since the discharge can be collected directly into the toilet or into a pail or pan as desired. There are more complicated means of irrigations called *colostomy irrigators* which can be used if the patient so desires. The simplest way of fastening a type of pad over a colostomy is to have a small web or elastic belt. This can be obtained for men as a wide athletic support of 6-inch width. It can be made from 6-inch elastic by anyone. In the female patients, an ordinary girdle will suffice. In the colostomy management, which is a real thing and which these patients learn to handle better than they can be taught, after a certain experience, all that is required is to change a small pad, a little piece of cotton or linen gauze twice a day. There is a little mucoid secretion which is the normal secretion that comes from any bowel that is exposed, and there will, of



course, be a little irritation from time to time of the exposed portion of the bowel, with a little bleeding. Neither of these is dangerous, however, nor are they difficult to take care of.

## INTESTINAL ANOMALIES

### Duplications of Alimentary Tract

—These are hollow structures which possess a muscular coat, usually of 2 layers, and are lined with epithelium similar to that found in some portion of the gastrointestinal tract or colon. These lesions are always contiguous to some portion of the alimentary tube, and in all but 1 case they were strongly adherent to it. The type of epithelium lining the duplication does not necessarily correspond to that part of the alimentary tract to which the structure is attached. Thus, a cyst of the tongue was lined by colonic mucosa, and a cyst of the rectum was partially lined with gastric epithelium. The cystic structure may or may not communicate with the adjacent intestinal lumen. In 2 cases observed by Ladd and Gross<sup>33</sup> there was such a communication, but in the 16 remaining cases there was no opening. An important finding is the histological fact that the muscular coats of the duplication are intimately adherent to and at times are microscopically an integral part of the muscularis of the alimentary tract.

The contents of a duplication vary with the type of epithelium lining the structure, with the presence or absence of a communication with the adjacent intestine, and with the presence or absence of necrosis of the duplication wall. Thus, if there is an opening into the bowel, the duplication contents will be similar to those of the adjacent intestinal tract. In general, however,

there is no communication with the intestinal lumen and the cystic structure contains a clear colorless fluid of mucoid consistency. In 2 specimens the cyst had reached such size that there was pressure necrosis and slough-

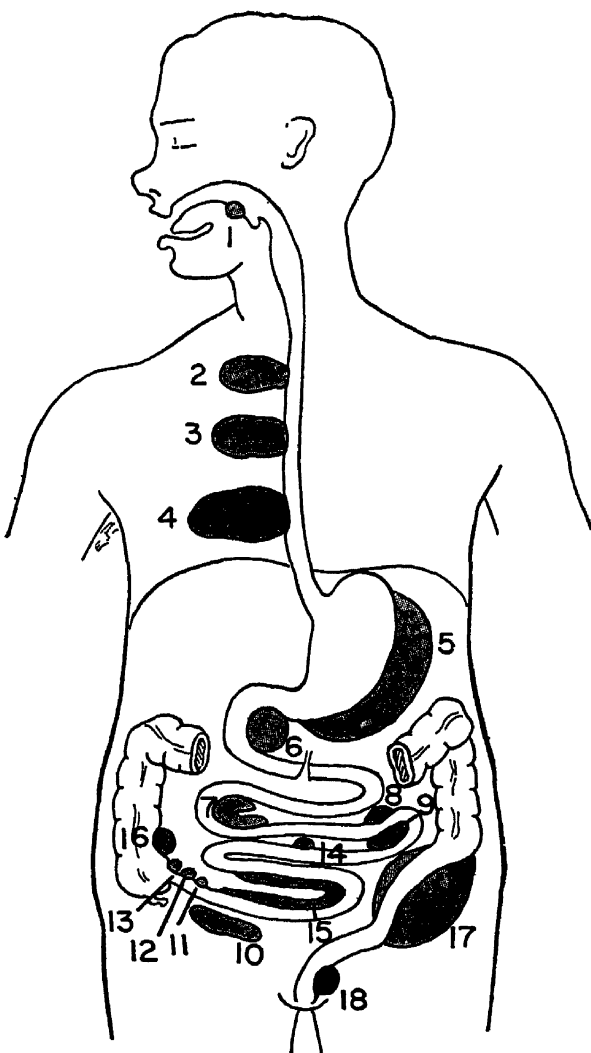


Fig. 9 — Chart showing distribution of lesions in 18 cases of duplication of alimentary tract. Number beside each lesion indicates patient as listed in table of cases. (Ladd and Gross: Surg, Gynec. & Obst)

ing of the lining membrane. The entrapped fluid, therefore, was hemorrhagic and murky-colored.

The size of the specimens is variable. It depends upon the ability of the lesion to expand into adjacent cavities or tis-

TABLE I.  
CASES OF DUPLICATIONS OF THE ALIMENTARY TRACT  
(Ladd and Gross<sup>33</sup>)

Case No.	Age	Position of Cyst	Size	Type of Mucous Membrane	Treatment	Result
1		Base of tongue	1 cm. in diameter	Colonic	Excision	Recovered
2	11 mos.	Right pleural cavity	4 to 5 cm in diameter	Gastric	Attempted excision	Recovered
3	2 yrs.	Mediastinum	10 x 6 x 5 cm.	Gastric	Excision	Recovered
4	7 mos.	Right pleural cavity	8 x 5 x 4 cm	Gastric	Excision	Dead
5	7 yrs.	Along stomach	As large as stomach itself	Necrotic	Marsupialization	Recovered
6	5 wks.	Duodenum	4.5 x 3.5 x 3.5 cm.	Duodenal	Resection, posterior gastroenterojejunostomy	Recovered
7	6 mos.	Jejunum	22 x 6 x 6 cm.	Gastric	Mikulicz resection	Dead
8	2 wks	Jejunum	4 cm. in diameter	Jejunal	Resection and anastomosis	Recovered
9	3 mos.	Ileum	7 x 4 x 4 cm.	Gastric	None	Dead
10	19 mos.	Terminal ileum	15.5 x 4 x 5 cm.	Columnar epithelium	Excision	Recovered
11	12 days	Terminal ileum	1 5 cm. in diameter	Ileal	Resection and anastomosis	Recovered
12	9 yrs.	Terminal ileum	1.2 cm. in diameter	?	Not yet treated*	
13	2 mos.	Terminal ileum	2 cm. in diameter	Ileal	Resection and anastomosis	Recovered
14	6 yrs.	Ileum	3 cm. in diameter	Ileal	Resection and anastomosis	Recovered
15	2 yrs.	Ileum	28 cm. long, 2 cm. diameter	Gastric	Resection and anastomosis	Dead
16	3 mos.	Cecum	4 cm. in diameter	Colonic	Resection and anastomosis	Dead
17	2 wks	Sigmoid	12 x 10 x 8 cm.	Ileal and colonic	Not treated	Dead
18	6 mos.	Rectum	5 x 2.5 x 2.5 cm.	Mixed	Excision, rectum repaired	Recovered

\* This cyst was discovered during operation for acute appendicitis and has not been removed.

sues before giving symptoms, and upon the presence or absence of a communication with the intestinal tube. In 1 case a cyst at the base of the tongue was about a centimeter in diameter, was lined by colonic mucous membrane, and was filled with a clear syrupy fluid. In 3 cases the structures were adherent to the esophagus and had ballooned out into the mediastinum and right pleural cavity. Hence, they had grown to orange or grapefruit size before at-

curred in the present series were as follows: Base of tongue, 1; esophagus, 3; stomach, 1; duodenum, 1; jejunum, 2; ileum, 7; cecum, 1; sigmoid, 1; rectum, 1.

It is important for the surgeon to recognize the pathological difference between duplications and mesenteric cysts. The latter are lymphatic in origin, have a thinner wall, and can be separated readily from adjacent viscera. This is in contrast to the dupli-



Fig. 10—Case 8. Photograph taken during operation showing a golf-ball-sized duplication of lower jejunum. Adjacent intestine compressed over one surface of cystic structure. Resection of cyst and adjacent intestine followed by lateral anastomosis with successful result (Ladd and Gross: Surg., Gynec. & Obst.)

tracting attention. One specimen which arose from the greater curvature of the stomach in a 6-year-old girl was almost as large as the normal stomach itself. The cystic lesions appearing along the duodenum, jejunum, and ileum, usually do not become larger than a golf-ball before producing symptoms. In Case 15 the structure was sausage-shaped, was 38 cm. long and 2 cm. in diameter, and ran along the mesenteric border of the terminal ileum. One duplication of the sigmoid was about the size of a large orange. Finally, in a 6-months'-old patient there was a cyst arising from the posterior rectum wall, which was somewhat larger than a plum. The levels at which duplications have oc-

curred, which has a thicker, muscular wall, and which can be disconnected from the intestine only with difficulty.

**Embryology**—There are many theories which attempt to explain the origin of these duplications. Those arising in the mid or terminal ileum previously were thought to be due to aberrations in the development of a Meckel's diverticulum. This theory, however, is no longer tenable. Twinning of an isolated portion of the embryo has been believed by some to be the causative factor. Sequestration, or a pinching off of a group of cells from the primordial intestinal tube, might well account for the development of nearby, closely-placed cysts, which fin-

ally attain all of the histological elements of the wall of an alimenteric tube. The most probable explanation is that advanced by Lewis and Thyng, who frequently found diverticula at various levels in the fetal alimenteric tracts of pigs, rabbits, cats, sheep, and man. Such outpocketings were most common in the ileum, a fact which suggests a relationship to the high incidence of duplications in the ileum. These knob-

by the writers was 2 weeks of age; the oldest was 9 years. The symptoms produced by these lesions may be grouped under 3 headings, *i. e.*, (1) obstruction of the alimentary tract by regional external pressure; (2) pain produced by distention of the cystic structure; and (3) hemorrhage because of interference with the intestinal blood supply, leading to sloughing of the intestinal mucosa.



Fig. 11—Case 4. Roentgenogram of duplication of esophagus which ballooned out into right pleural cavity. Cystic lesion outlined by arrows. Mediastinum and heart displaced to patient's left side. (Ladd and Gross: Surg., Gynec & Obst)

like outpockets of the intestinal wall, which are not related to Meckel's diverticula, normally regress, but the pinching off of 1 of these structures might well separate it from the normal intestinal wall and give rise to an adjacent duplication.

**Clinical Findings**—A duplication of the alimentary tract is usually observed in children. It may be seen in later life, but the nature of the process is one which attracts attention in early years. The youngest patient observed

In the lesion appearing at the base of the tongue, difficulty in swallowing was the outstanding symptom. With the cysts of the mediastinum and the right pleural cavity, there was esophageal compression and difficulty in swallowing, and there was interference with the proper expansion of the lung, which led to dyspnea. In the duplication of the stomach, in spite of the large size of the lesion, the adjacent gastric lumen was not compressed sufficiently to cause obstruction, and the patient's

primary complaint was related to epigastric fullness and pain produced by tenseness in the mass. Most of the cysts of the duodenum, jejunum, and the ileum brought early signs of partial intestinal obstruction characterized by colic-like pain, vomiting, increased peristalsis, and, finally, signs related to dehydration. In the long, tube-like duplication of the terminal ileum (Case

quickly led to constipation and abdominal distention.

Physical examination often gives important evidence concerning the position of the lesion and suggests the proper diagnosis. In a cyst at the base of the tongue the lesion can easily be palpated as a swelling below the foramen cecum. A thoracic cyst can be quickly suspected because of physical

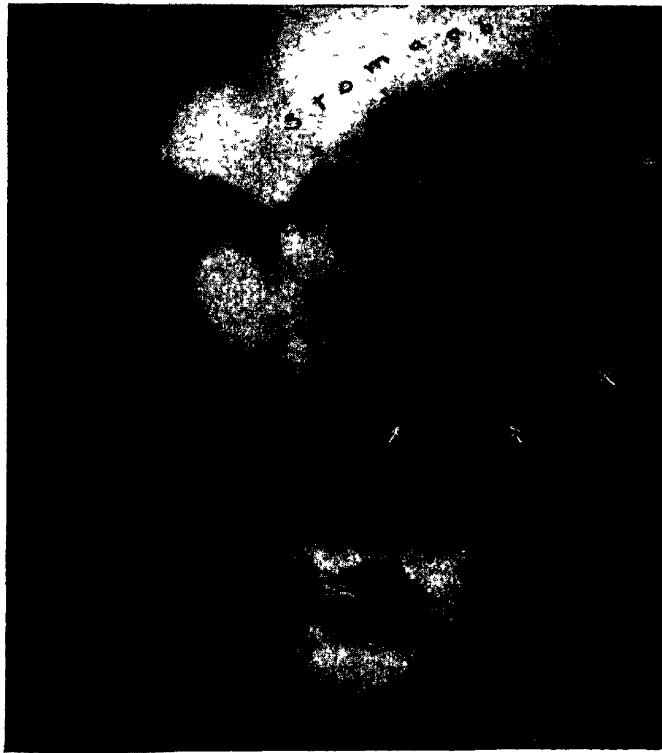


Fig. 12—Case 5. Roentgenogram of duplication of stomach showing large mass outlined by arrows beneath stomach. Stomach is filled with barium and is dented along its greater curvature by mass (Ladd and Gross: Surg., Gynec. & Obst.)

15), the primary complaints were related to severe painless hemorrhage from the lower intestinal tract, caused by ulceration and sloughing of the ileal mucosa. Two small cysts of the cecum have been encountered, 1 of which produced partial obstruction and the other, by bulging into the cecal lumen, served as the leading point of an intussusception. Finally, the cyst of the rectal wall (Case 18) produced early encroachment on the adjacent rectal lumen, and

signs of dysphagia, dyspnea, and pulmonary compression. The duplication of the stomach was of such a size that it easily could be palpated, running along in the direction of the greater curvature of the stomach. This mass lacked peristaltic waves and persisted after the evacuation of the stomach with a tube, and the cleansing of the transverse colon with an enema. The cysts of the duodenum, jejunum, and ileum could be palpated in practically every

ase. They were elastic, well-rounded, usually nontender, and except for the duodenal lesion, were quite freely movable within the abdominal cavity. In each of these cases, physical examination revealed some sign of partial intestinal obstruction. Such signs were noted as visible peristalsis, localized or

obstruction. The cyst of the posterior rectal wall could be palpated easily with a rectal examining finger; and although the lining of the rectum was smooth, it was displaced forward so that the examining finger could not be pushed up beyond the compressed point.

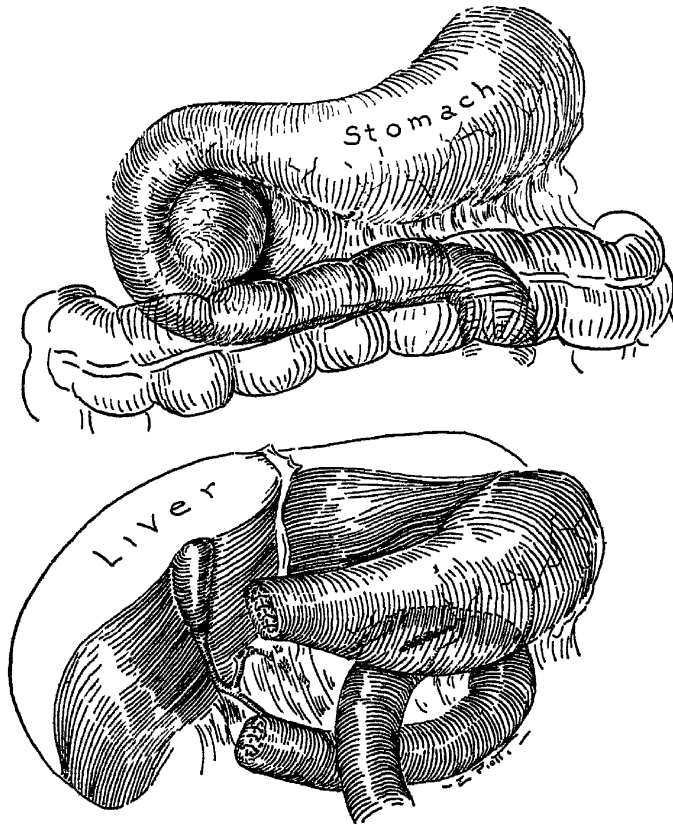


Fig 13—Case 6 Duplication of first and second portions of duodenum as found at operation. Lesion treated by excision of cyst and partial resection of duodenum supplemented by posterior gastrojejunostomy. Patient recovered. (Ladd and Gross: Surg., Gynec. & Obst.)

general abdominal distention, and increased audible peristaltic activity. The tube-like structure along the terminal duodenum in Case 15 could not be felt during examination of the abdomen, and there were no physical signs of intestinal obstruction. The only finding in this child was the presence of blood on the glove when rectal examination had been performed. The cyst of the sigmoid was freely movable, elastic, nontender, and without signs of colonic

**Roentgenological Findings**—Duplications in the *thorax* give roentgenographic findings characteristic of mediastinal neoplasms or cysts. In 1 case there was a large, well-defined lesion displacing the upper lobe of the right lung. In the other 2 patients there was a large, well-circumscribed, opaque mass without calcification, which apparently arose from mediastinal structures and then ballooned out into the right pleural cavity, to replace about

two-thirds of the lung area in the anteroposterior chest films. The density of such a lesion is rather uniform, due to its fluid content. The uniform shadow and the absence of calcification tend to distinguish it from a dermoid or teratoma. With some of the large lesions there may be a shift of the mediastinum

to surrounding viscera. Thus, a gastrointestinal barium series showed a large extrinsic mass along the greater curvature of the stomach, which smoothly bulged into the gastric lumen (Fig. 12). Following this examination, a barium enema showed the mass to displace the transverse colon downward without ap-

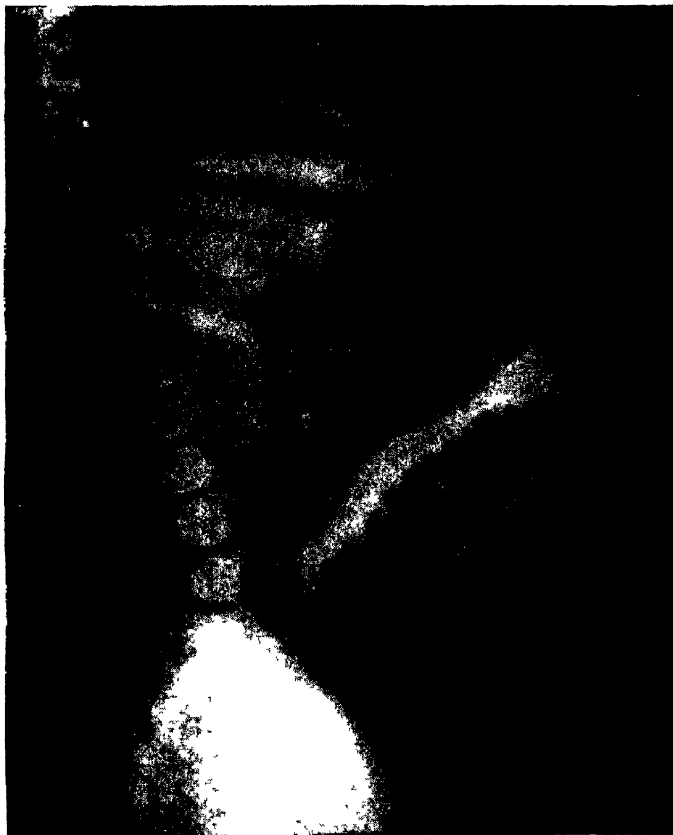


Fig 14—Case 7. Lateral roentgenogram of abdomen showing dilated intestinal loops, accumulation of fluid beneath loops, and marked abdominal distention. These findings indicative of obstruction which at operation was found to be caused by large duplication of lower portion of jejunum. (Ladd and Gross: Surg, Gynec. & Obst)

and heart to the other side of the thorax (Fig. 11), but it was surprising to find relatively little displacement in some of these cases. Lipiodol visualization of the bronchial tree shows marked compression of the lung on the involved side. In the patient with a duplication of the *stomach*, roentgenographic studies were of considerable aid in roughly outlining the size of the lesion and in determining its position with relation

preciable compression of this organ. With the *duodenal cyst* (Fig. 13) there was sufficient compression of the first and second portions of the duodenum to give evidence of partial obstruction at this level. The cystic lesions of the *jejunum* and *ileum* in some cases showed partial obstruction by x-ray visualization.

Usually as much could be learned from films of the abdomen in the

posteroanterior and lateral direction without contrast media, as could be determined with the use of a barium gastrointestinal series. Thus, distention of intestinal loops (Fig. 14), particularly if they are localized to 1 portion of the abdomen, are indicative of obstruction and may give some information concerning the level at which the lesion exists. The large duplication of the sigmoid (Fig. 15) showed a rounded

**Treatment** — Obviously, the treatment of this condition is surgical. Two important facts must again be stressed regarding the pathology of these lesions in relationship to operative procedures: (1) The cystic structure and the intestine have a common wall at 1 point, and the 2 cannot be dissected apart with safety; (2) the blood-vessels of the contiguous alimentary tube may course over the surface of the cyst,



Fig. 15—Case 17. Photograph of abdomen at autopsy showing cystic duplication (12 x 10 x 8 cm.) of sigmoid in a 2-weeks-old infant. Arrows indicate flattened sigmoid, 1, as it courses over surface of duplication, 2. (Ladd and Gross: Surg., Gynec. & Obst.)

area of rather uniform density with peripheral displacement of gas-containing viscera. A barium enema in such a case should outline the sigmoid as a flattened viscus, as it courses around the mass. In the cyst of the *posterior rectal wall*, roentgenographic examination was a great aid for 2 reasons: (1) It gave some idea of the size and superior extent of the lesion in the lateral field (Fig. 16); (2) absence of bony defect in lumbar and sacral vertebrae gave some assurance that the pelvic mass was not an anterior meningocele.

hence attempts at local removal of the cyst may induce ischemia and necrosis of the intestine. This latter consideration is particularly important in the treatment of the small intestine and of the sigmoid, in which the vessels from mesenteric or sigmoidal leaves spread out over the surface of the cyst.

In the lesion at the base of the tongue no difficulty was encountered in excising the mass completely, working through the oral cavity.

The *thoracic* lesions have given the greatest difficulty, from the point of



view of technical procedures, particularly in patients under 1 year of age. In every case an attempt was made to open the thorax through a posterior or posterolateral incision, to enter the pleural cavity and then free the cystic structure from the adjacent lung, a dissection which can easily be performed. On attempting to dissect away the cyst wall from the esophagus, however, the dangers of entering the esoph-

velop a fatal mediastinitis or empyema; whereas the recognition of the esophageal defect during operation allows the surgeon to make some provision for closing the defect or for treating regional infection which surely will develop subsequently. The poor results which have been obtained in these thoracic lesions, due primarily to the associated esophageal injury at time of operation, raises the possibility that



Fig. 16—Case 18. Lateral roentgenogram of patient with cystic duplication of rectum. Barium in rectum shows it displaced forward by mass lying in hollow of sacrum. (Ladd and Gross: Surg., Gynec. & Obst.)

ageal lumen are high. In 1 case the esophageal lumen was entered, and the surgical field was thereby transformed from an aseptic into a soiled one. On first consideration it would seem relatively easy to turn in the edges of the damaged esophagus, but it has been the experience of the writers that the closure thus effected heals poorly, and there is great danger of establishing an esophagopleural fistula. This possibility of injury to the esophagus must be stressed, because if the surgeon overlooks a small opening thus accidentally made, the patient will subsequently de-

these patients might be treated better by marsupialization of the cyst through the posterior thoracic wall, combined with subsequent destruction of the cyst lining by the use of necrobiotic agents which easily could be introduced through the fistulous opening.

The duplication of the *stomach*, as exemplified in Case 5, might be treated in several ways. First, a total or nearly total *gastrectomy* with establishment of an *esophagojejunostomy* would permit the removal of the cystic structure along with the stomach. This appears to be a rather extensive under-

taking, however, particularly in a young individual. This risk does not seem to be justified when simpler, more satisfactory forms of treatment are available. The authors were fortunate enough in their case to find a cyst so distended by accumulated secretory fluid that there had been sloughing of its entire mucosal lining. By simply *marsupializing* this duplication onto the anterior abdominal skin, therefore,

*terior gastrojejunostomy* was performed with satisfactory results. In those duplications of a cystic nature occurring between the *duodenum* and *cecum*, complete *extirpation of the mass* has been practiced along with *resection of the adjacent portion of the intestine*. This policy has been adopted because experience has shown that the mass cannot be enucleated without the danger of perforating the

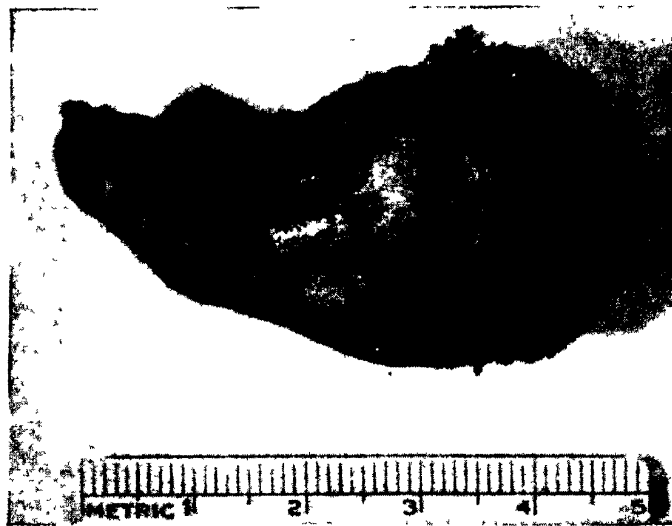


Fig. 17—Case 18 Photograph of duplication of rectum which was surgically excised. (Ladd and Gross Surg, Gynec. & Obst.)

the release of all entrapped fluid allowed the walls to fall together and to coalesce. If one should not be so fortunate in having the mucous membrane thus spontaneously destroy itself, 2 methods of treatment are open, either by *marsupialization* and subsequent *injection of sclerosing fluids*, or by the establishment of a large *communication between the cyst and the stomach* to permit drainage of the cyst contents into the gastric lumen.

In the patient with a *cyst of the duodenal wall* (Fig. 13), the *first portion of the duodenum and the mass* were *excised in toto*, the *ends of the duodenum* were *inverted*, and a *pos-*

*intestine* or leaving it in an ischemic state. In all cases, except 1, a *side-to-side anastomosis* was employed to re-establish the continuity of the intestinal tract, because end-to-end anastomosis of the small intestine in infants and children is technically difficult and may lead to disaster.

While it is the belief of Ladd and Gross that the most satisfactory outcome will be insured by surgical excision of the mass and local resection of the adjacent intestine, mention must be made of the publication of Gardner and Hart, who treated a *cystic lesion of the duodenum* by a *transduodenal approach* and *opened a large win-*

*dow from the duodenum into the cyst.* This allowed the cyst to empty its mucoid contents continuously into the duodenum. The success of this procedure in Hart's case suggests that it might be worth trying in cases where a short operative procedure is necessary because of the poor general condition of the patient. It must be pointed

out that the writers, therefore, again practiced *local resection* and establishment of an *ileocolostomy*. The large *cyst of the sigmoid* which was discovered at autopsy demonstrated again that it would be futile to dissect the cyst from the sigmoidal loop, and that the best method of treatment would be *excision of the mass*

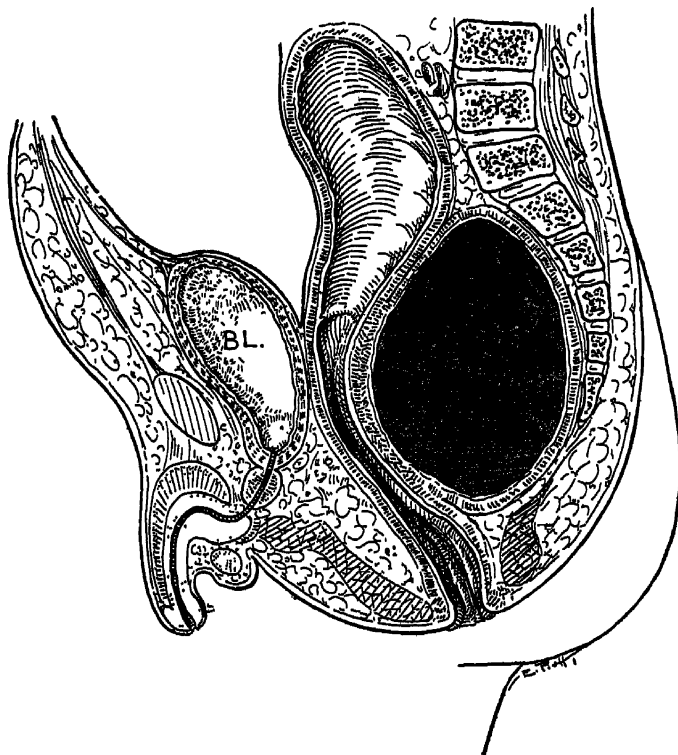


Fig. 18—Case 18. Reconstruction drawing showing duplication, anterior to sacrum and producing partial obstruction of rectum. Surgically treated by excision of cyst and part of posterior rectal wall. Rectum accidentally opened in excision of cyst. Suture of rectal defect followed by recovery. *BL.*—bladder; *R.D.*—rectal duplication (Ladd and Gross Surg, Gynec & Obst.)

out that stasis in such an outpocket from the intestine might lead to troublesome symptoms. Hence, the opening into the cyst must be adequate to insure proper drainage.

Cysts of *terminal ileum* or *cecum* may so impinge on the ileocecal valve that partial obstruction is produced. The 2 specimens encountered in this region demonstrated the impossibility of excising them from the cecal wall without injury to the remaining intes-

*and the adjacent gut, re-establishment of the colonic continuity*, possibly combined with a *temporary cecostomy* or *transverse colostomy* as a safety valve.

The *duplication of the posterior rectal wall* in Case 18 (Figs. 17 and 18) was first treated by the family doctor, who intermittently relieved the rectal obstruction by aspirating the cyst through a posterior sacral approach. Fortunately, infection did not occur.

Each time the cyst was aspirated it refilled in 5 or 6 days' time and again displaced the rectum forward in such a way as to obstruct its lumen. Operation on this 6-months-old baby was performed under *ether anesthesia*, with the child in the face-down position and the abdomen supported on a sandbag, so as to push the buttocks high up in the operative field. A curved incision, posterior to the anus, permitted displacement of the anus and anal sphincters forward. Then, by carrying the dissection upward in the midline between the levator ani muscles, the hollow of the sacrum was reached, and the cyst behind the rectum was exposed. Little difficulty was encountered in dissecting the cyst along its posterior, superior, and lateral surfaces, where good lines of cleavage were obtained. The cyst, however, was found to be extremely adherent to the rectal wall, and in the course of the dissection a large opening was made in the posterior portion of the rectum. The rectum was now repaired by turning it inward with 3 layers of interrupted, fine, chromic catgut sutures. A small rubber drain was led down into the hollow of the sacrum, and brought out through the skin incision. The rectal wall healed *per primum*. There was no suppuration in the perirectal spaces, and the child quickly recovered.

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## LIVER AND PANCREAS

By V. W. MURRAY WRIGHT, M.D.

### I. LIVER

#### Vitamin C in Liver Diseases —

Avitaminosis C causes certain complications in liver disease, according to Gonzalez Galvin.<sup>1</sup> Improvement may be obtained by the intravenous use of vitamin C in doses of  $\frac{3}{4}$  to  $1\frac{1}{2}$  grains (0.05 to 0.1 Gm.). According to this investigator, the results are satisfactory when given along with the proper treatment of the disease. In the patients observed by Gonzalez Galvin vitamin C therapy was able to control gastric hemorrhages due to liver insufficiency. It increased the diuresis in ascites due to cirrhosis; improved the general condition in patients with hepatitis associated with avitaminosis and also modified in a favorable manner the course of true toxic hepatitis. It is necessary that treatment be given over an extended period of time in order to obtain a satisfactory response. The use of vitamin C does not alter the course of cirrhosis and it must be admitted that the diuresis and the general improvement of patients with ascitic cirrhosis are but transient.

#### Traumatic Rupture of Liver

**Etiology** — Advancing civilization with its attendant speed-up of industrial activity and rapidity of transportation makes for more accidents, particularly serious ones. An increasing number of multiple fractures, crushing injuries, etc., are to be expected. Among such injuries, intrathoracic and intra-abdominal trauma will be increasingly evident. Lamb<sup>2</sup> reviews 60 cases of rupture of the liver and shows that it is most commonly due to violent injuries but that seemingly trivial injuries may likewise cause laceration. Rupture of the liver is much *more*

*frequent in young people* than in older ones. No doubt this can be accounted for on the basis of violence alone, for the young engage in many more daring activities than do the old. Another reason probably is that the bony protection in the young is much more supple and that minor blows therefore are more likely to reach the liver. It is interesting to note that every one of the *women* had sustained injury as a result of an automobile accident. Although the *men* had been injured in all sorts of accidents, most of their injuries had been produced by automobiles. One child fell while walking the curbing and struck his right lower ribs. Another coasted into a tree. Another was kicked in the side by a horse. A few were injured while playing games, chiefly football. The wheel of some *vehicle transversing the abdomen* was a common cause of injury. Falling from a height was the etiologic factor in a number of cases.

**Treatment**—For best end-results it is *absolutely essential to recognize* rupture of the liver *early* in order that proper care may be instituted promptly. Thöle states that the *mortality increases with each hour's delay* in treatment, and Lamb's statistics confirm this assertion. X-ray and laboratory studies are of little help and an exact diagnosis cannot be made except on exploration. Given a patient, however, who has met with a blow to the midtrunk and soon shows *signs of shock*, together with *tenderness in the right upper quadrant, rebound tenderness* (blood in the peritoneal cavity) and an elevated white cell count (bleeding in a serous cavity), an *exploration* is mandatory. It is of primary importance in treating such cases

that the patient should receive *whole blood* before, during and after operation in sufficient quantities *to keep the blood-pressure within the range of safety*. *Transverse incision* gives a better exposure for barrel-chested patients but is of doubtful advantage for thin patients. Depending upon the degree of damage encountered in the individual case, surgery will consist of *mattress sutures*, ligation or searing of oozing surfaces with the *actual cautery* or the *Bovie scalpel*. Tamponage with *hot gauze drains* not only aids in controlling hemorrhage, but is essential for postoperative drainage of either bile or infection. *Infection* after liver injury is *common*. Drainage of bile occurred in 50 per cent of the cases but ceased in every case by the third week.

The commonest *postoperative complications* were, in the order of frequency: Peritonitis, postoperative hemorrhage, subdiaphragmatic abscess, intrahepatic abscess, subhepatic abscess and abscess of the lesser peritoneal cavity. Before operation could be performed, 26 patients died. Of 34 cases operated on, 15 died and 19 recovered, a mortality rate of 44 per cent. For the entire series of 60 cases, however, the mortality rate was 68 per cent.

### Subphrenic Abscess

Between 1900 and 1938, according to Faxon,<sup>3</sup> 175 patients with the diagnosis of an infectious subphrenic process were admitted to the Massachusetts General Hospital. In 22 of these cases, undrained abscesses were found at autopsy; in 4, spontaneous drainage occurred. In 32 patients the clinical course with the physical signs and Roentgen findings suggested an irritative process below the diaphragm. These patients all recovered without surgical operation. Six patients were operated on, but no pus was found

at operation; presumably, these were suffering from a mild nonsuppurative type of lesion.

From a study of the age incidence and sex distribution in the 111 cases operated on there is an increase in the subphrenic abscess from the first to the fifth decade of life. Sixty-eight per cent of the cases occurred in men and 32 per cent in women. The majority of cases developed the subphrenic abscess by way of an extension of intraperitoneal sepsis. A certain number, however, occurred by way of the lymphatics and of the blood stream. Infection originating in the appendix is the commonest source of subphrenic abscess formation. Next in frequency as the original source of infection are lesions of the stomach and the duodenum, with infections in the liver and bile passages ranking third.

A subphrenic abscess should be suspected in any patient in which a persistent unexplained fever is associated with a history of recent intraperitoneal sepsis. In 87 per cent of the patients studied the abscesses were on the right side and in the posterosuperior space.

It is difficult sometimes to obtain a clear-cut picture from pressure over the twelfth rib posteriorly or the lower costal margin anteriorly in the early stages of development. Examinations frequently repeated, however, will finally demonstrate tenderness over the involved space in practically all patients.

When the diagnosis finally has been made the treatment indicated is prompt *drainage*.

According to Faxon, the transthoracic approach increases the risk of contamination of the pleural cavity and, therefore, the *retroperitoneal approach* is preferred. Contamination of the pleural or peritoneal cavities during the operation more than doubles the mortality rate. This occurs far more often with

the transthoracic and transperitoneal approaches than with the retroperitoneal operation

## II. PANCREAS

### Hyperinsulinism

**Treatment by Excision of Pancreatic Adenomas**—It is interesting that a Swiss surgeon, Sauerbruch,<sup>4</sup> credits American investigators with having recognized in recent years a form of paroxysmal spontaneous hypoglycemia caused by hyperfunctioning of a benign pancreatic adenoma. Removal of the tumor effects a cure. The clinical picture of hypoglycemia caused by a pancreatic tumor begins with a sensation of hunger, fatigue and faintness. The patient feels weak in the knees and collapses; there are apathy, loss of orientation, stupor and somnolence. General or localized spasms may appear. The pupils become dilated and lose their reactivity. There may be foaming at the mouth and biting of the tongue or lips, symptoms which might well be diagnosed as epilepsy. Similarly, the patients after awakening fail to recollect the event. They recover within a few minutes *if given sugar* solution to drink; the recovery naturally is even more rapid after intravenous injection of dextrose. The true nature of the condition is not recognized ordinarily until repeated determinations of the sugar content of the lumbar punctate and of the blood has been made.

An additional *important sign* of a pancreatic adenoma is the time of the appearance of the attacks. As would be expected, they generally appear in the morning, when the patient is still fasting, when he is hungry or after exertions or excitations, *i. e., always* when the blood sugar level is physiologically low.

**Early operation** is advisable. The detection of a tumor the size of a cherry

stone or a cherry may be difficult. Splitting of the cortical layer often is necessary. The pancreas is *exposed best through the gastrocolic ligament*.

Sauerbruch reports 2 personal cases and 2 from the literature, all of which had been cured by the extirpation of pancreatic adenomas and which he refers to as *insulomas*," inasmuch as others have reported that adenomas of the pancreas contain a high content of insulin and act as constant and uncontrolled reservoirs which result in hyperinsulinism.

### Hypoglycemia

**Treatment — Subtotal Pancreatectomy**—Partial pancreatectomy has been advocated by various surgeons for relief of persistent hypoglycemia when, on laparotomy, no tumors of the pancreas are found. David<sup>5</sup> reports the results of 18 partial resections (from 14 to 28 grams) with no tumor. In 15 patients the pancreas was normal histologically and in 3 hyperplasia of the islet cells was present. *In 14 patients* of this group the *minimal blood sugar was below 50 mg. per 100 cc.* Of 14 surviving patients, 3 were free from attacks, 3 were moderately improved, and the attacks continued in 8 cases. Seventeen other patients who presented no tumors had from 35 to 60 grams of pancreas removed for spontaneous hypoglycemia. The examination of the pancreatic tissue revealed 14 normal pancreases, hyperplasia of the islet cells in 2, and in 1 case a pancreatitis was present. The symptoms of hypoglycemia were relieved in 11 of these patients. There was only 1 operative death.

The author concludes that exploration of the pancreas is indicated in patients with the triad of symptoms described by Whipple (attacks of nervous or gastrointestinal disturbances coming

on in a fasting state; a hypoglycemia with readings below 50 mg.; and immediate relief from the ingestion of dextrose) in whom extrapancreatic causes of hypoglycemia have been excluded and dietary management has failed. David is of the opinion that subtotal resection of the tail and body of the pancreas up to the superior mesenteric vessels is indicated when exploration reveals no tumor.

### Acute Pancreatitis

**Treatment by Pancreatotomy**—According to Lewison,<sup>6</sup> 33 cases of acute pancreatitis occurred among 100,000 admissions between 1921 and 1939 to the Beth Israel Hospital. The author believes that its rarity may have been overestimated. The diagnosis of the 33 cases and 2 treated elsewhere was established or confirmed at operation. Cases of manifest chronic pancreatitis, acute pancreatitis secondary to primary processes elsewhere, acute pancreatitis resulting from perforation of a peptic ulcer and pancreatic calculi were not considered. Hemorrhagic, edematous, suppurative and gangrenous types of pancreatitis were distinguished and each requires individual attention regarding diagnosis, prognosis, prophylaxis and treatment. Pain and tenderness, usually in the epigastrium or the upper part of the abdomen, were constant clinical observations. *Radiation of pain to the back*, vomiting and a history of similar *recurrent attacks* were elicited frequently. Incision and drainage of the pancreas combined with 1 or more auxiliary procedures was carried out in 77 per cent of the cases. The operative mortality was 17 per cent.

### Pancreatic Cysts

**New Treatment**—Dissatisfied with the results of treating pancreatic cysts by simple marsupialization, Kafka<sup>7</sup> anas-

tomosed 2 cases to the gastrointestinal tract. One case died from a hemorrhage on the ninth day but the second case went on to a complete cure. In the first case, that of a woman aged 58 with a pseudocyst, a primary *pancreatocystogastrostomy* was made. While the wound appeared to heal satisfactorily from the surgical aspect, the patient succumbed on the ninth day after operation from a sudden hemorrhage into the intestinal tract.

The second patient, a woman aged 56 with a pseudocyst, was operated upon and a fistula in the cavity of the pancreas developed. Later a *pancreatocystojejunostomy* was performed with complete cure.

The author reviews the various accepted surgical methods and discusses the different types of *anastomosis*. All of these operations were regarded as palliative and free from danger.

The fatal outcome in the first case described by Kafka demonstrated the possibility of complications arising from the anastomosis of a pancreatic cyst to the intestinal tract. The author advises against a primary anastomosis of the cyst, especially with a lateral pancreatogastrostomy with external drainage of the residual cavity in the form of Jeddlick's operation.

Kafka calls attention to the fact that a *persistent fistula* may be *anastomosed with the gastrointestinal tract*. If a residual cavity is found upon Roentgen examination or at laparotomy, it may be handled by a wide cystenterostomy, since in this case the danger of obliteration of the stoma does not exist as in the presence of a simple anastomosis of the fistula of the gastrointestinal canal.

### Acute Necrosis of Pancreas

**Etiology**—Reporting a study of 134 cases of pancreatic necrosis, Reichl<sup>8</sup> de-



terminated that in all except 1 there were biliary disturbances with indigestion or biliary colic. He maintains, therefore, that pancreatic necrosis is a secondary disorder, *i. e.*, a sequel of inflammatory disease of the biliary system. He estimates that a primary biliary disorder is the cause of pancreatic necrosis in more than 90 per cent of the cases. This applies to *genuine necrosis* of the pancreas only and not to cases in which an external cause, such as operative trauma or *Ascaris*, is the causative agent. At the author's clinic, the cases of pancreatic necrosis amounted to only 12 per cent of the total number of biliary disturbances.

**Diagnosis**—It is suggested by Weyeneth and Wassmer<sup>9</sup> that pancreatitis should be considered in the presence of an acute abdominal syndrome if the history reveals an old or a recent disorder of the hepatobiliary or gastroduodenal tracts, and particularly if the patient is obese or addicted to alcohol. The face of the patient with pancreatitis is generally pale or somewhat cyanotic. If the biliary passages are involved, the appearance is subicteric. The patient sweats profusely and complains of vertigo and trembling of the fingers. Vomiting is frequent, at first of food and later of bile. The abdomen often shows *supraumbilical distention*. The pain is extremely violent and is localized in the left half of the epigastrium. Although of considerable diagnostic significance, the symptom pain is not sufficient to establish the diagnosis.

**Treatment**—Opinions are divided as to expectant conservative therapy or surgical intervention, according to Reichl.<sup>8</sup> Of 89 patients, or 46 per cent operated on at the author's clinic, 41 died, whereas of 31 on conservative treatment, only 4, or 13 per cent, died. Ten patients hospitalized while in a grave or moribund

state died within a few hours or on the same day. It would appear, therefore, that *conservative treatment in the early phase* of acute necrosis of the pancreas is indicated while preparing the patient for *later operation*.

*Conservative treatment* consists of *interdiction of food intake* for from 3 to 4 days, *morphine* for pain, *antispasmodics*, *stimulation of intestinal peristalsis by drugs*, and *warm moist applications and heat to the abdomen*. The heart and circulation are supported by the parenteral administration of *isotonic fluids* and by *strophanthin - dextrose - strychnine* therapy.

If the patient recovers on the conservative regimen, *operative intervention* on the biliary tract should be resorted to from 4 to 6 weeks later, in order to *remove the contributing cause*. The operation consists of the *removal of the gall-bladder* and of a *supraduodenal choledochotomy* if the common duct contains *calculi* or is *dilated or inflamed*. The choledochus is carefully explored for stones, the papilla is dilated and the duct is irrigated. In order to relieve the pressure on the biliary tree, a Nélaton catheter is sutured into the duct and is left in place for from 10 to 14 days, after which time it can be removed without injury to the duct or causing a fistula. During the past several years, operations on the pancreas itself in the acute stage have been rejected by the author.

Of 26 cases observed by Weyeneth and Wassmer<sup>9</sup> at the surgical clinic of Geneva, 5 of the patients were treated conservatively and improved. Of 20 subjected to surgical treatment, 17 died. They were operated on during the acute phase. The 3 patients who survived the operation had been operated on about 2 weeks after the onset. The authors are

convinced that operation leads to toxic shock instead of exerting a favorable influence on the condition.

The treatment successfully employed in 5 cases was the following: (1) *Strict abstinence from food and liquids*. (2) *Restriction of chlorides for 48 hours*; this is done in spite of the hypochloremia in order to diminish the pancreatic edema. (3) Daily administration of from 1 to 2 quarts (liters) of 10 per cent *dextrose solution* by intravenous infusion and from 15 to 30 units of *insulin*. (4) Large doses of *atropine* to diminish the pancreatic secretion. (5) Relief of the intestines by repeated *enemas*. (6) *Icebag* to the epigastric region and *morphine*. *After the acute*

*phase* has passed (in 4 to 6 days), *fruit juices and carbohydrates* can be given. *Later*, the biliary passages can be examined and, if necessary, an *operation* on the biliary tract may be performed in order to prevent recurrences.

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## STOMACH

By JAMES NORMAN COOMBS, M.D.

### Peptic Ulcer

**Healing of Peptic Ulcer**—Regardless of the method of treatment applied in a given case of peptic ulcer, proof of healing or lack of it is essential. Few ulcers are treated in the early stage and the chronic ulcer with the consequent pathologic changes makes healing more difficult and even when obtained, permits defects to remain that induce recurrence. That peptic ulcer can be healed is a proved fact. Some ulcers heal without treatment. Many can be cured with diet, rest and medication. Cash<sup>1</sup> points out that the prevalence of ulcers that have undergone repeated courses of treatment without improvement or have reactivated after a period of quiescence is evidence of possible weakness in some phase of treatment.

Expectancy in the probable rate of healing of an ulcer with or without slough and exudate has no fixed rule.

The majority of active ulcers tend to heal readily, especially gastric; also some duodenal ulcers react to treatment with equal facility. Large active chronic ulcers usually react to direct treatment and heal readily, while the small shallow type often persist, and this type is frequently encountered in the chronic ulcer patient who has suffered varied experiences. Delay occurs more often with the ambulatory patient and is apparently due to excess food, with resulting increased gastric secretion and traumatism. Proof for this statement is that, when treatment of similar cases is given in bed, healing occurs in normal time.

A braid stain, after disappearance of free blood, exudate and even the crater, indicates that either unhealed scar tissue persists or that a turgescient pylorus with probable hypertrophy is present, or that the gall-bladder is involved or a severe form of duodenitis may be the source of

the persistent braid stain. Location of the stain in relation to pyloric constriction of the braid and the degree of braid constriction will aid in determining where the pylorus is hypertrophied and persistently spastic. When a positive braid stain is obtained before treatment and both tube returns (the procedure of removing slough, exudate and blood from the crater with the use of a tube with fenestrations which are brought in contact with the lesion by measurement taken from the positive test braid) and the x-ray examination are negative, careful study of the case will be required. A positive test braid alone or with tube returns, following surgical closure of a perforated ulcer, indicates an unhealed condition.

Proved healing, if followed by recurrence, aids in deciding the need for surgery. In suspected cancer of the stomach or when ulcers have doubtful cancer features, progressive and proved healing exclude such a possibility. After proved healing of a peptic ulcer, digestive symptoms may continue or more likely recur. Hyperacidity, supersecretion, gastritis, duodenitis, pyloric involvement, chronic appendicitis, cholecystitis, gastric hyperesthesia, disease of the colon, adhesions, chronic partial duodenal obstruction, gastroenteroptosis, poor dietetic hygiene, vicious habits, use of alcohol and tobacco are frequently associated with peptic ulcer and may remain and cause symptoms.

**Perforation of Peptic Ulcer** — All available contributions on acute perforations, besides a mass of unpublished material in England and abroad, have been examined by Jennings.<sup>2</sup> He presents evidence that distinct groups of ulcer cases exist, that their incidence varies independently, that the present common type of pyloric ulcer was relatively uncommon until recently, and that

its increase is a true increase and not merely the result of better diagnosis and hospital service. In this extensive review the author emphasizes that too much attention has been paid to the constitutional factor in peptic ulcer and not enough to environmental causes.

The history of uncomplicated ulcers is obscured by changes in fashion in diagnosis and in the selection of patients admitted to the hospital or coming to necropsy. The history of perforated ulcer can be reconstructed from available records in several countries. Between 1850 and 1900, of every 6 free perforations into the peritoneal cavity, 3 affected young women under 25, 1 an elderly woman, 1 an elderly man and 1 a young man. Since 1920, of every 10 perforations, 1 has affected an elderly woman and 9 men, mostly in the middle years or younger. Perforations in young women form a sharply defined group, which increased rapidly at the beginning of the XIX Century and died out completely and suddenly at the beginning of the XX Century, the same changes taking place at about the same time in Germany, France, Scandinavia and the English-speaking countries. This type of ulcer must have been due, therefore, to something in the environment or in the mode of life.

*Perforated pyloric ulcers in men* can also be shown statistically to fall into at least 2 independent groups. One group is closely associated with lesser curve perforations. It has a similar incidence to that of perforation in women since 1920. The other group tends to affect younger men and has recently undergone a large increase in northwest Europe and presumably throughout the English-speaking countries. Owing to increased facilities for admission to the hospital and other factors, it is impossible to measure this increase directly in

France, Germany, Italy, England and the United States, but there is evidence that in parts of Sweden the increase is from 300 to 600 per cent. This estimate agrees with the change in ratio from 2 men: 1 elderly woman, to 10 men: 1 elderly woman, which has taken place in several countries. It follows that something in the mode of life is also responsible for this type of perforation.

It is impossible to find sources of information in western Europe or in the United States which would enable changes in incidence or *uncomplicated ulcer* to be estimated. Uncomplicated ulcers therefore cannot be proved to fall into the same categories as perforated ulcers, but there is indirect evidence that they do. The author urges that perforated peptic ulcers and many other so-called constitutional diseases should be notified. Thus accurate statistics should be compiled for cases of acute perforations and if such statistics were available for transition periods, they would probably be of great service in elucidating the mechanism and in a campaign of prevention.

**Diagnosis**—A review of the diagnosis, treatment and results in 152 cases of *acute perforated peptic ulcer* treated surgically at the St. Louis City Hospital during a period of 6 years is presented by Kelly.<sup>3</sup> All the patients were either on relief or unemployed. There were 124,317 general admissions to the hospital during the 6 years under study, giving an incidence of 0.0012 per cent of perforated peptic ulcers. Most of the perforations occurred in the middle years of life. All patients 70 or more years of age died. The number of cases that occurred during the 4 seasons was approximately the same, there being only a slight, but insignificant, increase during the spring and fall months. Only 7 patients were women, 4.6 per cent. This

ratio of men to women compares favorably with many other reports. A history of previous gastric disturbance was given by 128, or 84.2 per cent, of the patients. This fact indicates that previous gastric disturbances are a valuable aid in diagnosis.

The *duration of symptoms* varied from 7 days to 55 years. Twenty-four patients experienced the pain of perforation as the first symptom of the gastric disturbance. No relationship was found between the duration of ulcer symptoms before perforation and the mortality rate. When the patient first experienced the pain of perforation, it was described by 62 as being in the epigastrium and general abdomen. The next most frequent location of the pain was in the epigastrium alone, 52 times. Generalized abdominal pain was described by 23 patients. Fifteen patients described their pain as occurring in the middle or lower part of the abdomen or at the upper right quadrant; 113 vomited after the perforation and before operation, while 39 did not vomit. A study of the symptoms of perforated gastric and duodenal ulcers indicates that an anatomic location of the ulcer cannot be made from the history of the perforation. An acute perforation constitutes a surgical emergency and delay in operation increases the mortality rate.

**Treatment**—The simplest and quickest operation should be performed in acute perforations and the operation of choice is *simple purse-string closure*; frequently a *tab of omentum* was *sutured over the closure*. This procedure is used with the view in mind of preserving the life of the patient and seems to be attended by the least mortality.

**Results of Treatment**—Only a small percentage of cases necessitated secondary operations, thus justifying the pro-

cedure. Of the 140 cases in which operation was performed, *drainage* was instituted in 102 and the mortality rate was practically the same in the 2 groups. Thirty-nine, or 27.8 per cent, of the 140 patients operated on died. A post-mortem examination was made in the 12 cases in which operation was not done. Three of the patients who were not operated on were more than 71 years of age and were in a moribund state on entry. They died soon afterward. Four were in extremely poor physical condition on entry and supportive measures were instituted, but the patients did not rally enough to justify operating. One patient who died shortly after admission did not have a diagnosis until the post-mortem examination. Four incorrect diagnoses were made. The average stay in the hospital for the patients who recovered was 25.1 days. Of the post-operative deaths, 51 per cent occurred within the first 3 days.

A follow-up was made on 57 of the 101 patients discharged. A patient was considered as having a good result if he was entirely free from pain and was able to work. A few of these patients remained on a diet. If the patient at times had pain which was easily controlled by a diet, the result was considered as fair. If ulcer symptoms were constant the results were considered poor. By these standards, 43 were considered as having a good result, 10 a fair result and 4 a poor result.

***Incidence of Hemorrhage Occurring with Perforation in Peptic Ulcer***—The impression that bleeding ulcers do not perforate and that ulcer perforations do not bleed has been generally accepted by physicians and surgeons as true. Finsterer in his vast experience reported the simultaneous occurrence of hemorrhage and perforation only 3 times. Blackford and his

associates concluded that bleeding ulcers do not perforate and ulcer perforations do not bleed. This conclusion, however, was questioned by James Matheson, who reported hemorrhage in the presence of perforation.

Winters and Egan<sup>4</sup> reviewed the literature on this subject and found that in the cases reported the occurrence of hemorrhage varied from 1.5 to 18 per cent, with an average of 8 per cent, and they stated, "Whether or not one is to defend the statement that bleeding ulcers do not perforate and ulcer perforations do not bleed depends greatly on what history can be obtained from the patient." They report the records of cases of perforated ulcer at the Cook County Hospital from 1925 to 1938, inclusive, which were studied to determine the incidence of hemorrhage. The question of hemorrhage itself was also studied because the amount of bleeding from an ulcer varies. Patients who bleed severely enough to cause faintness, syncope, tachycardia, asthenia, pallor, and signs of shock, are usually sufficiently alarmed to see a physician immediately. In general, the amount of hematemesis when estimated by the patient is too frequently greatly exaggerated. The question of melena is different. The quantity of blood can in no way be determined accurately. From a study, however, of a volunteer, who went on hourly milk and cream feedings for 21 days, and took measured quantities of whole human blood at 3-day intervals, it was found that approximately 60 cc of blood would give a stool indisputably tarry in color and consistency.

During the 4-year-observation period there were 361 patients admitted to Cook County Hospital with a diagnosis of perforated peptic ulcer. The greatest number of perforations occurred in the fourth decade, whereas bleeding with

perforation reached its highest incidence in the sixth decade, approximately 20 years after the incidence of the greatest number of perforations. Either general or localized arteriosclerosis is the most probable cause for this variation. One hundred and fifty-two perforated ulcers were found in the stomach and in this group there were 16 perforations accompanied by bleeding. In addition there were 188 perforated ulcers found in the duodenum, again with 16 bleeding perforations. Thus, of 361 patients with perforation, 36 bled. Fourteen of the 56 patients with hemorrhage and perforation had a history of bleeding for from 1 to 6 days prior to perforation. In the majority of the patients, the bleeding was determined by the character of the stool. A few patients, however, noted hematemesis. Nine patients had some bleeding from 7 to 14 days before perforation.

From this study, the authors concluded that a patient with a known ulcer history who suddenly manifests signs of hemorrhage should be looked upon as presenting a graver complication of ulcer, *i. e.*, perforation.

### Chronic Gastric Ulcer

**Surgical Treatment**—Walters and Clagett<sup>5</sup> report 272 consecutive cases of chronic gastric ulcers in which operation was performed at the Mayo Clinic and were followed for from 1 to 5 years. There were 220 men to 52 women, or a ratio of about 4.5:1. The majority of the lesions developed along the lesser curvature close to the angle of the stomach. The major complication to which gastric ulcer, but not duodenal ulcer, is subject, is malignant change. The authors believe that all gastric ulcers must be treated surgically if they fail to respond promptly to medical management. When the symptoms have been of short

duration, the lesion small and uncomplicated, and the patient less than 40 years of age, medical management may be indicated. If the pain is relieved, the blood disappears from the stool, and the niche, on x-ray examination, disappears, the patient may be considered to have a benign ulcer. The patient must continue medical management at home, however, and undergo x-ray re-examination at least every 3 months. If at any time there is any evidence that the lesion has not remained completely healed, surgical exploration should be advised.

Surgical treatment of chronic gastric ulcer is almost always indicated if the symptoms have been of long duration or have not responded to adequate medical management. Likewise, operation may be indicated if the symptoms are severe and disabling but of short duration. Surgical intervention is indicated in cases of bleeding, perforating and obstructing gastric ulcers. *Posterior Polya resection* was used for 131 of the 272 patients, *knife or cautery excision of the lesion combined with gastroenterostomy* was used in 50 cases and other procedures were used much less frequently but in some cases to good advantage when resection or excision and gastroenterostomy were not feasible. Only 1 patient of the 162 who answered the questionnaires classified himself as having a poor or unsatisfactory result. This patient had had a simple excision of the ulcer, a procedure which is not recommended.

The *results* were approximately equal for all types of surgical procedures, indicating that the operation be fitted to the patient. Gastroenterostomy without excision of the gastric ulcer seemed to give the least satisfactory results. On some occasions, however, no other procedure is advisable or technically feasible. There was only 1 case of possible bleeding fol-

lowing operation and no cases of gastrojejunal ulcer were definitely proved following any of the procedures performed; however, some patients in each group at times had some mild distress. Disturbing symptoms or recurrence of ulceration is seldom encountered following operation.

**Results of Gastroenterostomy in Gastric and Duodenal Ulcers**—The results obtained as well as the method of study used by Church and Hinton<sup>6</sup> in 106 cases of gastroenterostomy on an average of 7.1 years after operation are significant.

The patients made a total of 2694 visits to the clinic, an average of 25.4 visits each. Any merit this report may have lies in (1) a continuous personal contact between the patient and physician, which resulted in the recording and studying of all complaints; and (2) the frequency of roentgenological studies. Church and Hinton have adopted the policy of making roentgenological examinations of each patient every 6 months. This personal follow-up method showed that statistics obtained by correspondence are of questionable value. For example, 1 patient in the series reported himself in a letter as "well," but the reports of another hospital showed re-operation for a recurrence. When the results are unsuccessful, the patients do not return and do not respond to follow-up letters. Experience in this study has shown that the patients must be traced to their homes at frequent intervals if accurate data are to be obtained.

This material of 106 patients contained 96 males and 10 females with an average age of 38 years and preoperative ulcerations for 5.6 years. About 40 per cent of the patients were Irish, Italians, or Russians. There were 94 duodenal and 9 gastric ulcers, the site of the ulcers in 3 patients not being given.

The *indications for surgery* were as follows: severe pain; obstruction; perforation; pain and obstruction; pain and hemorrhage; obstruction alone; pain, hemorrhage, and obstruction; hemorrhage alone; and obstruction and hemorrhage. Malignant degeneration is a definite threat in all ulcer patients and although it may be considered an indication for surgery, the authors were not very enthusiastic in using this as a compelling cause for operation.

The *results of surgery* showed that 24.5 per cent of the patients could be considered cured and 29.2 per cent benefited, making a total of 53.7 per cent who benefited. No benefit was obtained in 46.2 per cent, however, and 17, or 16 per cent, of this group required secondary operation for recurrence of symptoms. Of the 106 patients, 20, or 18.8 per cent, had proved gastrojejunal ulcers, with an average time of appearance of 3½ years. Hemorrhage occurred preoperatively in 15 patients (14.1 per cent), but in 91 of the operated patients who did not have preoperative hemorrhage, 15 (16.5 per cent) subsequently developed postoperative hemorrhage. In 19 cases of obstruction treated by gastroenterostomy, 8 (42 per cent) were cured, 4 (21 per cent) were benefited, and 37 per cent were not benefited. This obstructed group included 3 cases of marginal postoperative ulcer, an incidence of 15.6 per cent.

The authors conclude that the results in their series "did not produce so favorable a view of this operative procedure as is generally presented by other authors, presumably because of the longer follow-up period adopted."

### Benign Gastric Tumors

According to Myhre,<sup>7</sup> benign gastric tumors, which he classifies as epithelial and not epithelial, are relatively frequent.

The epithelial tumors (adenomas and adenopapillomas) occur far more frequently than the not epithelial type (myomas and numerous other forms). A few cases of aberrant pancreatic remnants in the stomach wall have been reported and are classified as not epithelial tumors. The *epithelial tumors* may be solitary or few. In some cases they line the stomach wall. Most of them enter under the concept of a polyp, where a number of the not epithelial forms also belong because of their macroscopic appearance. The polyp form is ascribed to the action of peristalsis on the tumor. Epithelial tumors are often accompanied by gastritis and anacidity and not infrequently undergo malignant degeneration. Other important symptoms of benign gastric tumors are hemorrhages, constriction and invagination of the stomach. Many cases are latent or partly so and are accidental discoveries at necropsy. Diagnosis must depend on x-ray examination, made with especially careful technic, and on gastroscopy. Some of the small tumors, also larger angiomas, when very soft, can be established only by gastroscopy. Four cases are described in which gastroscopy was done.

### Gastric Carcinoma

Gastric cancer from a morphogenic point of view is discussed by Ewing.<sup>8</sup> The author admits that this is medical speculation but hopes that it may suggest something of the etiology of early gastric cancer. Certain constitutional factors which may influence its incidence, such as heredity, must be eliminated. Early gastric cancers appear in several varied forms which suggest entirely different modes of origin and exciting agents. Any attempt, therefore, to simplify their causation is likely to fail.

(1) Congenital abnormalities (misplaced portions of gastric or intestinal mucosa and tissue rests of the pancreas and adrenal) give rise to a small proportion of gastric cancers. For the development of these cancers it seems unnecessary to introduce other factors than those inherent in the growth potentialities of misplaced and embryonal cells.

(2) A number of gastric cancers develop on polypoid adenomas. The etiological problem is identical with that of gastrointestinal polyposis. Here a notable hereditary element, in addition to a special susceptibility of the mucosa to react to chemical irritation or infection by atypical changes in the superficial cells and polypoid outgrowths, exists. This group of cases invites investigation of the chemical and bacterial character of the gastric contents.

(3) Another group of gastric cancer is combined with pernicious anemia. Usually a small tumor arises in an atrophic mucosa and an atrophic stomach, and both are the results of the atrophic gastritis. The ultimate etiology must be traced back to the causes of atrophic gastritis.

(4) The relations between ulcer and cancer of the stomach are rather close, quite obscure and as yet unexplained. These cases present multiple lesions, usually in association with hypertrophic gastritis and sometimes with an atrophic mucosa. Excavation of a gastric adenocarcinoma, giving rise to ulcer and cancer in the same stomach, has been demonstrated. Under these conditions the appearance of precancerous changes on the edges of the ulcer can be accounted for, but these precancerous or preulcerous lesions would not be the result of the ulcer but the cause of the ulcer. Such lesions, if they escaped ulceration, owing to low digestive activity, would go on to fully developed cancer, where, if diges-





Fig. 1. Gastritis.



Fig 2. Erosive gastritis



Fig. 3. Gastrojejunal ulcer at site of anastomosis.

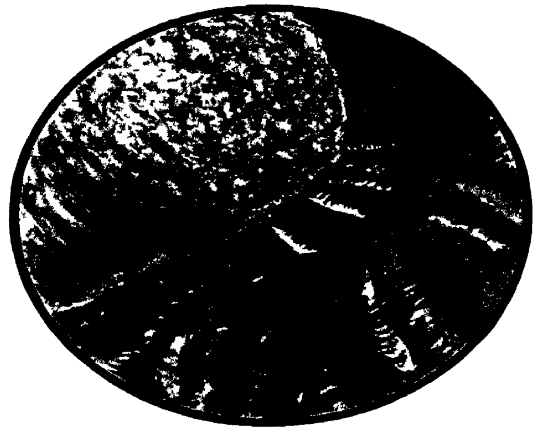


Fig. 4 Carcinoma at site of anastomosis.

Gastrosopic Observations in Cases of Gastric Distress Following Operations on the Stomach. (Moersch and Walters: Surg., Gynec. and Obst.)



tive activity were high, ulceration would supervent and the lesion would become a peptic ulcer. Gastric ulcers do not all arise in this manner but it seems probable that some do, explaining some of the peculiar combinations and assumed transformations between ulcer and cancer in hypertrophic gastritis. An active cancerogenic agent is suggested in such cases. A possible relation to avitaminosis should be considered and the gastric mucosa in cases of the Plummer-Vinson syndrome should be studied.

(5) Pyogenic infection cannot stand as a specific cancerogenic agent but it does figure in the appearance of carcinoma in chronically infected wounds. While bacterial infection probably may not be included among the direct exciting causes of gastric cancer, it should not be neglected as a contributing cause which affects its course.

(6) The gastric cancer which arises exclusively from the chief cells lining the fundi of the glands while the duct cells remain intact, produces most of the cellular small cell, diffusely growing, and highly malignant gastric carcinomas. Some functional stimulus affecting the functioning cells of the glands seems to be a reasonable hypothesis. The great frequency of gastric cancer is not surprising. The organ is exposed to the mechanical burden of excessive quantities of food and drink, to wide variations of heat and cold, to a multitude of chemical irritants in the ingestants, to insults from powerful medicaments, to a multitude of pathogenic and saprophytic bacteria and to regurgitation of foreign digestants in bile and pancreatic fluids, and at the same time it is required to maintain nearly constant functional activity.

**Symptoms** — The chief difficulty in the successful treatment of cancer of the stomach is that nearly two-thirds of the patients seek surgical help only after the

disease has become inoperable. Walton<sup>9</sup> points out that in many patients the symptoms may be of only 2 or 3 weeks' duration and the condition found inoperable when advice is first sought. It must be remembered that a gastric ulcer practically never starts after the age of 40 years. A patient of this age or beyond with a negative history and complaining of dyspepsia should be regarded as a cancer possibility until the contrary is definitely proved.

Carcinoma of the stomach may be divided into 3 separate groups, *i. e.*, (1) cancer of the cardiac orifice, (2) cancer of the pyloric orifice, and (3) cancer of the body of the stomach; the latter forms the largest group. It should be remembered that carcinoma of the cardiac or pyloric orifice generally leads to obstruction and these symptoms may entirely mask the underlying cause. When the growth is located in the cardiac orifice the patient develops symptoms of difficulty in swallowing. This history is steadily progressive and the obstruction is marked at first only for solid foods but later there is great difficulty in the swallowing of liquids. In a patient of 40 years of age, such symptoms usually mean carcinoma either of the esophagus itself or of the cardiac orifice of the stomach. Cancer in the body of the stomach may produce symptoms arising very suddenly and very deceivingly. The onset may occur with a large hematemesis and such patients have frequently been treated for many months or weeks for a supposed ulcer until the cancerous growth was hopelessly inoperable.

**Diagnosis** — In Walton's series of gastric carcinoma there were 112 cases which presented the history and symptoms of a previous gastric ulcer. The greatest reliance, from a diagnostic standpoint should be placed on a careful clinical history and followed up by careful

clinical investigation. Accessory methods of clinical investigation include the presence of occult blood in the stools and in the test-meal, especially if the blood persists. The presence of achlorhydria is suggestive but it may occur with a simple gastritis. Careful screening and x-ray examination is of great value but it should be undertaken by a skilled roentgenologist. Gastroscope in the difficult cases may also be of great value.

In a study of 444 patients with cancer of the stomach between 1919 and 1938, Abrahamson and Hinton<sup>10</sup> show that 296 or two-thirds were inoperable on admission. After clinical and x-ray examination, 148, or one-third, were considered operable. Even in this group, however, exploratory laparotomy proved in 69 cases that no operative measure could be undertaken. In only 24 cases, or 5.4 per cent of the total and 16.2 per cent of the 148 operable cases, could gastric resection be done, the only method providing hope for affecting a permanent cure in gastric carcinoma. Thus, the outlook at present is a dismal one, since the largest number of cases in which the diagnosis is made are already in an inoperable stage. Often when operability still exists, resectability is impossible.

The most dependable confirmations of diagnosis are the x-rays, the gastroscope and the gastric test-meal. The latter is the simplest and may be repeated at frequent intervals at relatively little expense. When examination shows a declining gastric acidity, the suspicion of carcinoma must be entertained and disproved. X-ray studies of the stomach should be made with greater frequency in suggestive cases and in those with undiagnosed and vague manifestations. X-ray examination of these patients is necessary, not to verify an already made

clinical diagnosis, but for careful search where there is no evidence of only minimal evidence of gastric disturbance.

The technic of gastric resection has been perfected and further operative refinements cannot offer hope for lengthening the life span of patients with gastric carcinoma. Their hope resides in the development of a means of diagnosis which will permit surgical intervention when the lesion is pathologically young rather than early in the clinical course. Until more specific tests are developed, each patient should have the benefit of such methods as are at present available. Faithful use of the test-meal, the x-rays and the gastroscope may help to disclose early carcinomatous lesions. The knowledge of the present dark outlook for the patient with carcinoma of the stomach should be disseminated among all practitioners and students of medicine.

Advance in the Roentgen diagnosis of gastric cancer has been due largely to the recognition of the fallacy or inadequacy of the following common concepts of the condition: (1) That it inevitably means a disease of utmost gravity and of very short duration; (2) that the continuous loss of both appetite and weight is a cardinal and unfailing symptom; (3) that, because of the usual and prolonged absence of pain, the patient generally seeks the advice of his physician and of the x-ray specialist only when it is already too late for curative surgery; (4) that an early x-ray diagnosis is, therefore, only an exceptional possibility.

Ledoux-Lebard<sup>11</sup> cites several cases in detail in evident contradiction to such dogmas and emphasizes the great diversity of the clinical picture and the utter impossibility of a merely clinical diagnosis of incipient gastric cancer.

Although progress in roentgenological technic has solved many of the problems of the early recognition of gastric cancer, some still await solution, and the author believes that better and more objective teaching is needed to reach this solution. Early diagnosis of benign lesions, which frequently are precursors of malignant ones, plays an important rôle. The knowledge gained regarding gastric ulcers and the malignant degeneration of some of them has been of great value. The size, site, shape, and contour of the niche often tend to prove its real nature. Gastric cancer frequently starts as a localized ulceration or infiltration, and the latter at first produces a sort of step of limited denivelation on the small curvature. This may not be evident fluoroscopically, but serial films may demonstrate it quite conclusively. Even before the "meniscus" sign is apparent, the infiltrated and stiff portion of the stomach wall is often limited by deeper steps and seems "fitted into" the wall of the stomach. The permanence of such an image is highly suspicious of cancer.

The Roentgen picture may be more valuable and a more certain factor of diagnosis than sight and touch. The findings of the surgeon at operation may be deceptive unless checked by histological section. The possibility of error after thorough Roentgen examination in competent hands is relatively small and the dangers of operation in those cases are more than offset by fatalities from unrecognized cancer. In questionable cases, test treatments may be instituted but if the Roentgen picture remains unchanged or progresses during such treatment even though clinical improvement occurs, the diagnosis of malignancy would appear to be established and the need for gastrectomy be indicated.

**Treatment**—In considering the surgical treatment of gastric cancer it must

be remembered that without surgery the patient is condemned to death. No other method of treatment offers any hope. Walton advises operation in every case in which there is no gross evidence of metastases, and even if metastases are present a *radical resection* may afford the patient 1 or more years of comfortable existence. Many large tumors may prove at operation to be removable. In the writer's series of 572 cases of gastric cancer, however, such a removal was possible in only 224 cases, *i. e.*, about 39.1 per cent. It seems probable that the capability will be extended for this disease as surgeons gain more experience. Resection should be as wide as possible including all lymph-glands draining the affected areas.

The writer's operative mortality averages about 30 per cent. There were 57 cases of simple anterior gastroenterostomy done as a palliative means to relieve the obstruction, yet this simple operation was associated with a mortality of 42 per cent. When simple exploratory laparotomy was carried out, the mortality averaged approximately 18 per cent. *Gastroenterostomy* should be recommended to those patients with a definite pyloric obstruction. Occasionally a *gastrostomy* seems justifiable for cases of cardiac obstruction.

**Preoperative and Postoperative Care**—According to Pack and Scharnagel,<sup>12</sup> the present success attending the surgical treatment of gastric cancer is due not only to improvement in operative technic but also to a better knowledge of the preoperative and postoperative care of the patient.

**Preoperative Care**—Patients with gastric cancer are nearly always suffering from such complicating conditions as dehydration, malnutrition, anemia, gastric dilatation, and retention due to pyloric obstruction.

Dehydration and malnutrition are frequently present in candidates for gastric surgery because of vomiting, or abstinence from food and fluids for fear of pain or discomfort. Fluids are preferably given by mouth, if retained, but supplementary fluid is administered by parenteral routes.

In order to establish a high glycogen reserve *glucose* is given, and it has been shown that when it is given orally it produces a higher and longer sustained blood-sugar elevation than when administered by the intravenous route. Sugar may be given as *honey*, *lactose* in *orange juice*, or in other ways, up to the night before the operation. Ten per cent glucose solution (5 oz.—150 cc.—to 1 oz.—30 cc.—of strained lemon juice) may be given in 6-ounce (180 cc.) feedings every hour during the day up to within 6 hours of the operation.

Many patients with gastric cancer have achlorhydria or low gastric acidity. The antiseptic value of the hydrochloric acid is of definite value to the patient. From 30 to 60 minims (2 to 4 cc.) of *dilute hydrochloric acid* may be given in water 3 times daily.

Anemia may result from gross *hemorrhage* due to gastric cancer or from long-continued small hemorrhages. If the hemoglobin is below 40 per cent, *blood transfusion* should be employed preoperatively. Frequently it is necessary to give a postoperative transfusion.

The relief of *dilatation* due to pyloric obstruction demands a chemical study of the blood, with the administration of *normal saline solution* or *Ringer's solution* when necessary to maintain the level of the blood chlorides.

*Constant suction* for decompression of the stomach by *the method of Wangensteen*, accompanied by the drinking of from 4 to 6 quarts (liters) of *fluid* daily is of great value. However, hypo-

chloremia must be especially guarded against if this treatment is continued for several days.

**General Postoperative Care** — The postoperative course depends largely on the nature of the operation, the skill and ease of execution, and the efficient preoperative preparation of the patient. Sufficient *carbon dioxide* (10 per cent) *and oxygen mixture* is given by inhalation for 15 minutes hourly for the first 8 or 12 hours. This ventilation of the lungs is continued by encouraging *deep breathing* of the patient. *Codeine*,  $\frac{1}{2}$  grain (0.03 Gm.), is permissible every 4 hours for 2 or 3 doses. In the experience of the authors, it has seemed wise to permit a certain degree of restlessness of the patient, provided suffering is not too intense.

In the afternoon following the operation, the Trendelenburg *position* of the bed is changed to a quarter sitting position. A *warm enema* may be given after 24 hours.

Puestow has shown that morphine, eserine, and prostigmine increased the peristalsis in the small bowel and paralyzed the large bowel. On the other hand, pituitrin and pitressin increased the peristalsis in the large intestine and paralyzed the small intestine. No drug was found which stimulated both the small and large intestines. In the selection of drugs for postoperative use, the surgeon, therefore, must choose the proper one to increase the tonus of either the large or the small intestine in which the gas accumulates. *Morphine*, when used, is the most effective stimulator of the motor activity of the small intestine, but it should be followed by *enemas* and, later, if necessary, by *pitressin* to overcome stasis in the large bowel.

*Dextrose solutions* are useful both to replenish the glycogen supply of the liver and to furnish nourishment. Five

per cent solution of dextrose in water is an isotonic solution and is used chiefly to combat dehydration. More concentrated solutions of dextrose (from 10 to 50 per cent) are hypertonic and are eliminated fairly rapidly; they act as a diuretic. **Hartmann's solution** has the same constituents as Ringer's solution with the addition of sodium bicarbonate and dextrose. This buffer solution serves to restore the water balance and chlorides, and replenish sodium, potassium, and calcium ions in proper proportions. It is especially indicated for pyloric obstruction, intestinal obstruction, and gastric and intestinal fistulas.

**Postoperative Complications—**(1) *Pulmonary Complications*—The duration of the anesthesia is of great importance and a longer anesthesia than 1½ hours greatly increases the incidence of pulmonary complications. The most important influencing factor, however, is the type of operative procedure. Operations on the stomach and duodenum are followed by pulmonary complications in a considerable number of patients. Embolism of the pulmonary artery, aspiration, and hypostatic pneumonia are frequently noticed.

Massive collapse of the lung occurs in about 1 per cent of operations for gastric cancer. It may be partial or complete. Shock of varying degree may complicate the picture. The treatment of shock is, first and foremost, the avoidance or prevention of the predisposing causes. Treatment cannot be specific because the causes are not known. An attempt may therefore be made to replace the blood volume and produce capillary constriction. **Blood** is the best solution with which to replace the volume of circulating fluid. Saline solutions are of little value, since permeation of these fluids through the capillary walls will lead to further interference with the

oxidation in the tissue. Ten per cent **dextrose**, even though the effect of its hypertonicity is temporary, is probably the best solution with which to replace the blood volume if blood itself is not available. Such drugs as adrenalin, adrenal cortex, or caffeine have very little value in this condition.

(2) *Acute Dilatation of Stomach*—This complication may occur after any operation on the stomach and usually takes place during the first 48 hours. It is most important that the condition be recognized early. The stomach will be found to contain an amount of fluid far in excess of the fluid intake. Bile is present practically always in considerable amounts. Thorough and early **lavage of the stomach with warm water** until the gastric return is clear is frequently a life-saving procedure. A **Levine tube** introduced through 1 nostril is left in place to provide continuous drainage and decompression of the stomach for from 12 to 24 hours. **Eserine** or **prostigmine** may be given hypodermically every 3 hours for 3 or 4 doses.

(3) *Gastric Hemorrhage*—This usually occurs within the first 24 hours after resection and is manifested by an appreciable amount of red or black blood in the vomitus. The **stomach** must be **lavaged** and **morphine** given in generous amounts. The **parenteral administration of fluids** or, better still, **transfusions of whole blood** are of great value.

(4) *Postoperative Peritonitis*—This complication is the cause of from one-fourth to one-tenth of the fatalities after gastrointestinal surgery. It may result from unavoidable contamination or from badly infected gastric contents, or it may be due to gross leakage of the gastric contents from defective anastomoses, perforation elsewhere in the gastrointestinal tract, gangrene and necrosis, from an

impaired blood supply, or from a suppurative focus of the wound.

### Sarcoma of Stomach

In a report of 7 cases of gastric leiomyoma, Lahey and Colcock<sup>13</sup> show that these tumors, while classed as benign lesions, have a marked tendency to undergo malignant degeneration. Symptoms of obstruction are often present. Surface ulceration of these tumors, which are predominantly intragastric, produces hematemesis or melena.

When a search for the cause of bleeding discloses multiple tumors or extensive involvement, sarcomatous degeneration always should be suspected. The experience of the authors shows that a *high subtotal gastrectomy* should be performed, including a wide margin of gastric wall. *Total gastrectomy* should be considered in advanced lesions involving the entire stomach.

According to Madding and Walters,<sup>14</sup> sarcoma of the stomach presented no typical picture, and only a few of the patients afflicted gave what is known as the classical history for neoplastic involvement of the stomach.

Because of the proximity of the submucous plexus of nerves, *pain* is a very common feature. It was found to be present in all cases of reticulum-cell sarcoma studied. This pain was either generalized over the abdomen, or, more often, was situated in the midepigastrium. In some instances the story was typical of peptic ulcer. The pain, however, did not respond as well to the usual measures for the management of ulcers, and, in addition, the periodicity of pain which so often accompanies the latter lesion was absent. Some patients complained of belching, anorexia, epigastric nocturnal pain, and loss of weight and strength.

The duration of symptoms ranged in the cases of reticulum-cell sarcoma from 2 months to several years, but, as a rule, the course was shorter than that of malignant lymphocytoma and carcinoma. The average duration of symptoms in cases of reticulum-cell sarcoma in which the patients were found to be inoperable was 37 months.

Gastric analysis (Toepfer's method) showed achlorhydria in 67 per cent of the cases of reticulum-cell sarcoma; normal acids were found in 20 per cent; and free acid was present, but in subnormal amounts, in 13 per cent.

Roentgenological examination failed to lead to the correct diagnosis in any of the cases, from which it is reasonable to conclude that, roentgenographically, there are no absolutely characteristic or diagnostic features of the lesion. The roentgenological diagnosis most often made was "carcinoma," but the roentgenographic examination was important as an index to the operability of the lesion.

Sixty-five per cent of the patients with reticulum-cell sarcoma had metastatic lesions as contrasted with 70 per cent of those with malignant lymphocytoma.

*Surgical treatment* has relatively more to offer to patients having sarcoma of the stomach than to those having carcinoma. Until the advent of radiation therapy, the treatment was the same for both conditions, *i. e.*, an attempt at radical extirpation.

In comparing the figures of the group of patients having reticulum-cell sarcoma with the group having malignant lymphocytoma, the authors found that the latter have the better life expectancy. The patients having malignant lymphocytoma who were treated with surgery alone had an average life of 5.6 years postoperatively, as contrasted with 3.6 years for the group treated by surgery followed by radiation. In the group of



patients having malignant lymphocytomas, 56 per cent were still living when last heard from. Two of these patients were living and well 14 years post-operatively, and 1 died 7 years post-operatively of pyelonephritis; at necropsy no evidence of the tumor was found. For only 1 of the patients with a 14-year cure, was Roentgen therapy used as an adjunct to surgery in the treatment.

The authors believe that a patient having malignant lymphocytoma (small round-cell lymphosarcoma) has a better prognosis than a patient having reticulum-cell sarcoma.

Fifty-six per cent of the patients who had malignant lymphocytomas are still living, as compared with 41 per cent of the patients alive who had reticulum-cell sarcomas. Eighteen per cent of the patients who had leiomyosarcomas and 62 per cent of those who had fibrosarcomas are still living. The number of patients in this series is perhaps too small to permit formation of any statistical conclusions.

The authors conclude that malignant lymphocytoma is an uncommon condition but that in contrast to the general opinion held, reticulum-cell sarcoma and lymphocytoma appear to have a better prognosis than the group consisting of leiomyosarcomas and fibrosarcomas. Reticulum-cell sarcoma and malignant lymphocytoma are as insidious in their development as carcinoma, and neither lesion seems to offer a greater probability of reaching the surgeon in an early and operable stage.

In the stomach, the radical operability was low, and differential diagnosis to distinguish the lymphosarcomas from carcinoma was impossible. On the basis of the histories at the clinic, it seemed safe to conclude that both reticulum-cell sarcoma and malignant lymphocytoma remain localized for some time. Thus, a

radical cure by *total extirpation* is possible, and this should be the goal in every instance.

It seemed evident from the malignant lymphocytomas which were found to be inoperable that *radiation* played a part in prolonging the life of the patients. This, however, was not true in respect to the inoperable reticulum-cell sarcomas, of which there were only 2 cases. It would seem, on the strength of this survey of a group of patients having sarcoma of the stomach, that it is highly desirable and practicable to perform an exploratory operation and to obtain a biopsy, even for patients in whom the clinical evidence points strongly to the presence of an inoperable growth. A differentiation of the 2 types of so-called lymphosarcoma may then be made and patients having malignant lymphocytoma (small round-cell lymphosarcoma) may be given the benefits of *Roentgen therapy*.

### Surgery of Stomach

**Methods and Results of Treatment of Cardiospasm**—The treatment of 52 patients (31 women and 21 men) during the past 16 years by various methods for cardiotonic esophageal dilatation is described by Wachs.<sup>15</sup> The former purely surgical treatment was replaced by the *bloodless Starck sound dilatation method* because of the excellent results obtained by the latter procedure. The treatment of choice at present remains the bloodless sound dilatation, which is one of the most useful procedures and, therefore, is entitled to first place as the most justifiable method for treating cardiospasm. Only after failure of the dilatation method due to cicatricial stenosis, or to the impossibility of introducing the cardiodilators through markedly sinuous or diverticulous indentations of the esophagus, are operative

interferences indicated. Sixteen patients were treated operatively, *i. e.*, 1 by a **temporary gastrostomy** as an emergency operation; 2 by **Heller cardiomyotomy**; 4 by **cardioplasty**; and 9 by **Hevrovsky gastroesophageal anastomosis**. The last-named method unquestionably yielded the best results, anatomically and functionally. All these

mal organ. Good results may also be obtained by the Heller cardiomyotomy. It is striking, however, to note in the literature reports of a comparatively high rate of recurrences following the Heller operation. The results of the plastic operations were not especially favorable, functionally nor anatomically. All of the patients retained deglutitional annoy-

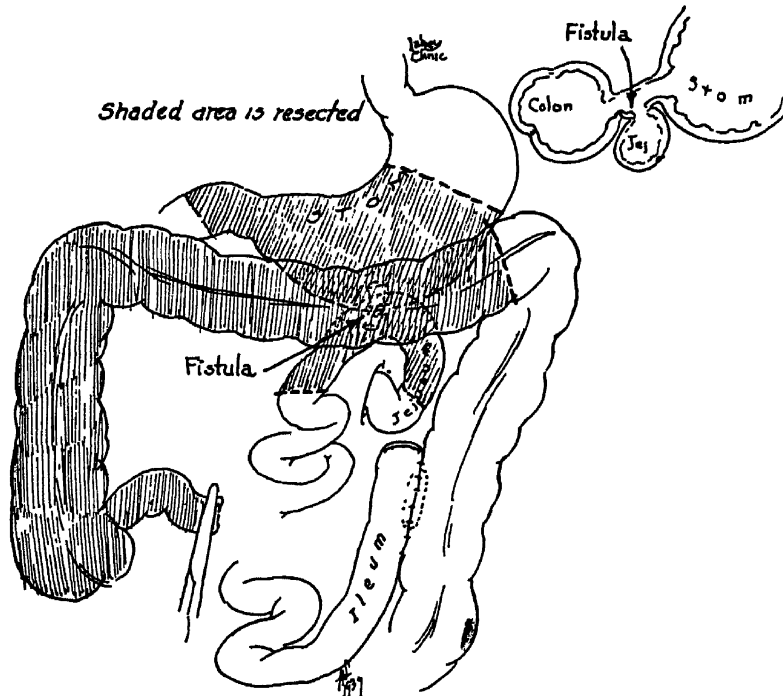


Fig 1—Gastrojejuncocolic fistula. Method of surgical management, first stage of operation. Terminal ileum is divided and ends of bowel closed by inverting sutures. Lateral anastomosis made between proximal loop of divided ileum and portion of colon distal to fistulous communication. Shaded area of stomach and intestine illustrates portion to be resected at second stage. Insert shows relationship of fistula to stomach, jejunum and colon. (Lahey and Marshall: *Am. J. Digest Dis*)

patients (the operations were undertaken in 1 patient 14 years ago; in 3 cases 11 years ago; 10 years ago in 3 cases; and in 1 a little over 1 year ago) remained symptom-free and able to work. None of them ever had return of the dysphagia.

The Roentgen re-examinations also revealed a permanency of the dilated esophagus without any tendency toward contractions, thus proving this as the best method for assuring a nearly nor-

ances; their Roentgen reports showed the esophageal dilatation nearly unaltered and a great expansion of the same still in evidence. Twenty-six patients, whose ages ranged from 17 to 58 years, were treated with the **Starck inflexible dilator**. The results were very good, even excellent, in 14 patients. These patients have absolutely no dysphagia symptoms and are really cured. The cures apparently lasted 6 years in 2 of these patients, 5 years in 3 cases, 4 years in 3

others, 4 years in 2 patients, and 2 years in 2 other patients. The results of the dilatation method in 10 patients were good without a doubt. These patients, however, complain of an occasional dysphagia, but remain able to

If the cure following the dilatation method, however, is judged by the Roentgen plates, the results would not be so favorable. In some of the patients the esophagus resumed a nearly normal contour after bloodless dilatation of the

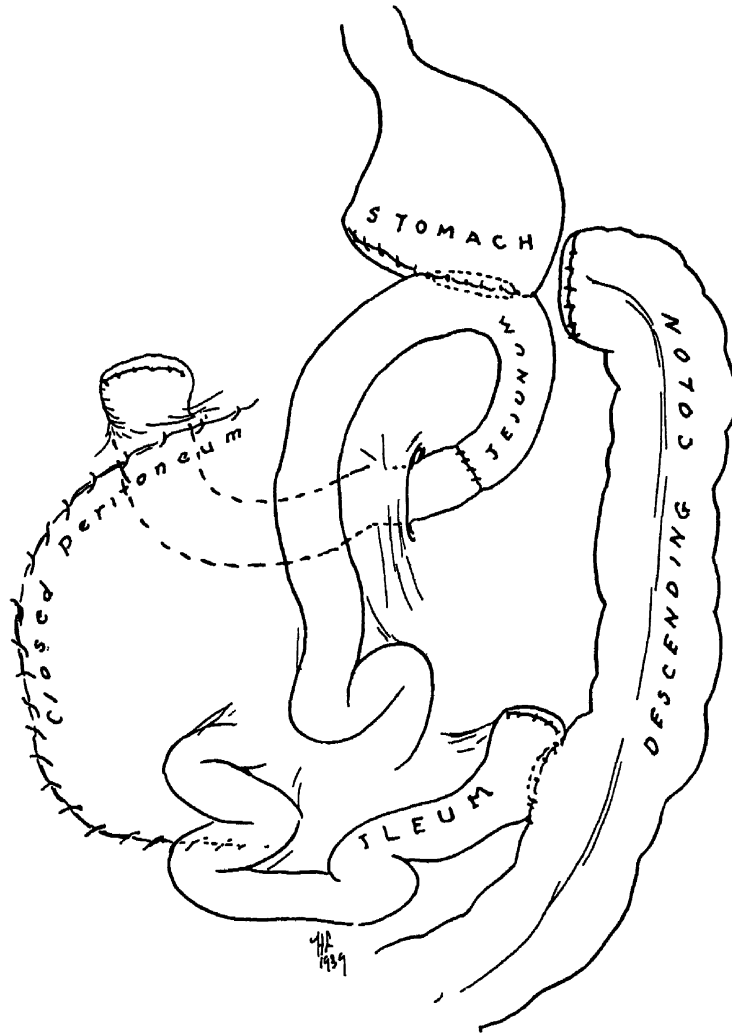


Fig. 2—Gastrojejunocolic fistula; second stage of operation, operation completed. Right colon and transverse colon to a point beyond fistulous tract resected. Involved jejunum excised and end-to-end anastomosis of jejunum done. High resection of stomach of Hofmeister type completes operation. Involved viscera removed in 1 block (Lahey and Marshall *Am J Digest Dis*)

work and do not show any signs of nutritional disturbances. It is acknowledged that following the bloodless dilatations, the expanded esophagus does not shrink materially in some patients, yet this treatment left the patients entirely free from all symptoms of dysphagia.

cardia. No unfavorable result after dilatation treatment was ever observed in the clinic; but 2 patients that were treated before entering Wachs' service were lost because of perforation of the esophagus by a consequent mediastinitis. Occasionally ruptures of the esophagus resulting from the bloodless dilatation treatment

were reported; therefore, this treatment should not be classified as nonhazardous even though the danger is practically minimal when compared with the dangers of operative procedures.

the fact that a return to the *dilatation sound method* is again the vogue Martin has recommended and employed this method for 40 years, obtaining good and lasting results in numerous patients. It

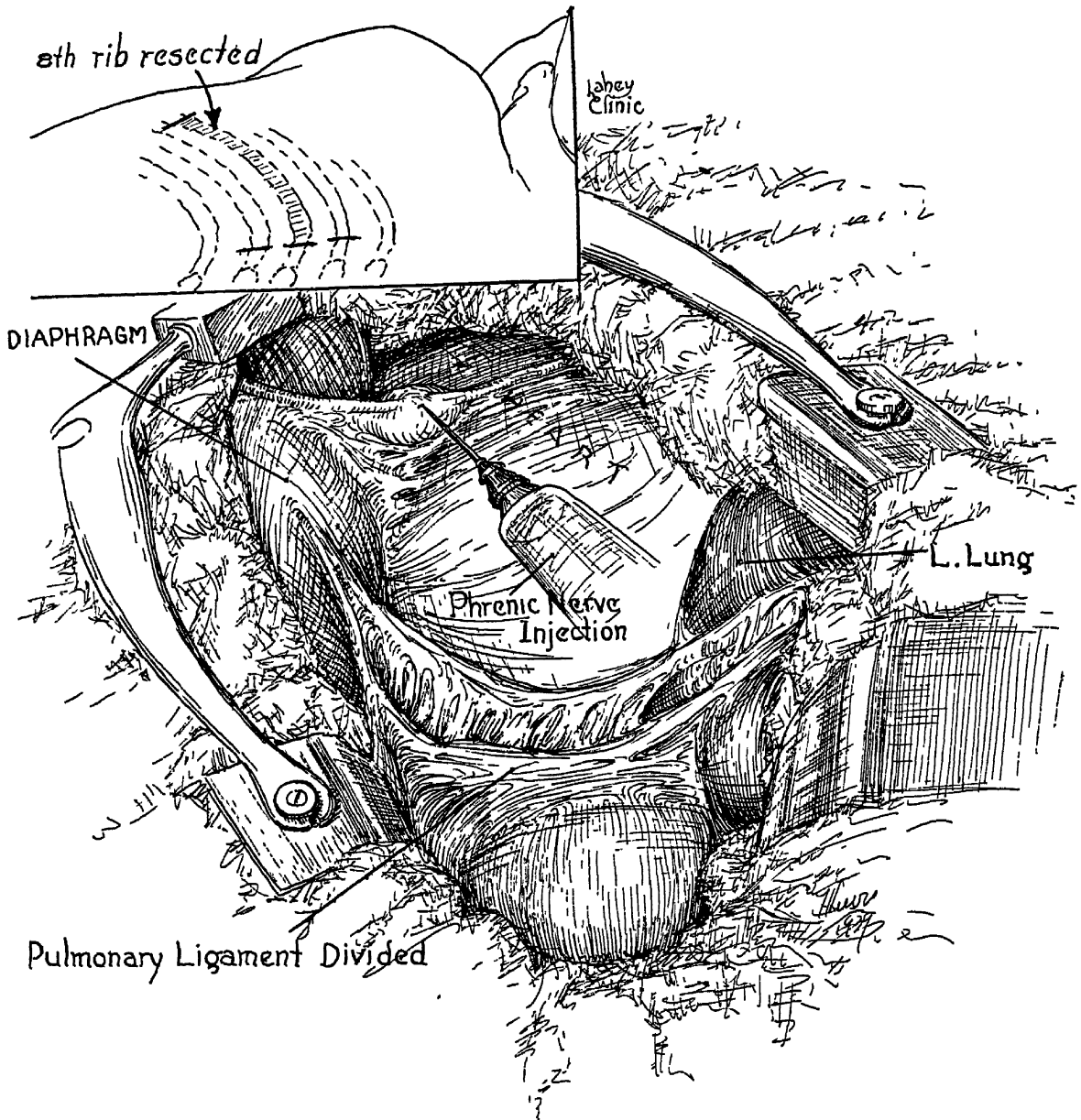


Fig. 3—Carcinoma of esophagus, lower third. Operation, transthoracic resection. Left thoracic cavity opened through infrascapular incision. Insert—Eighth rib resected and seventh and ninth ribs divided posteriorly. Inferior pulmonary ligament divided and left lung retracted, exposing diaphragm and mediastinum. Left phrenic nerve infiltrated with novocain solution, 2 per cent. (Lahey and Marshall: Am. J. Digest. Dis.)

In the discussion, Martin was glad to note that after cardiospasm has been treated with all the various surgical methods, the author's report established

made no difference to him whether the dilation sound of Gottstein or of Starck was used, the result was essentially the same. Both are good.

In the more unusual cases in which the small sounds cannot be forced through the esophagus, a *gastrostomy* is done to maintain nourishment; then the employment of fine buckshot and thread, according to *von Hacker's method of*

status, and it will remain normal if the sound treatment is repeated at regular intervals, this will also prevent the appearance of stenosis. Prevention of stenosis is the main issue, as this means no recurrences. This positive statement is

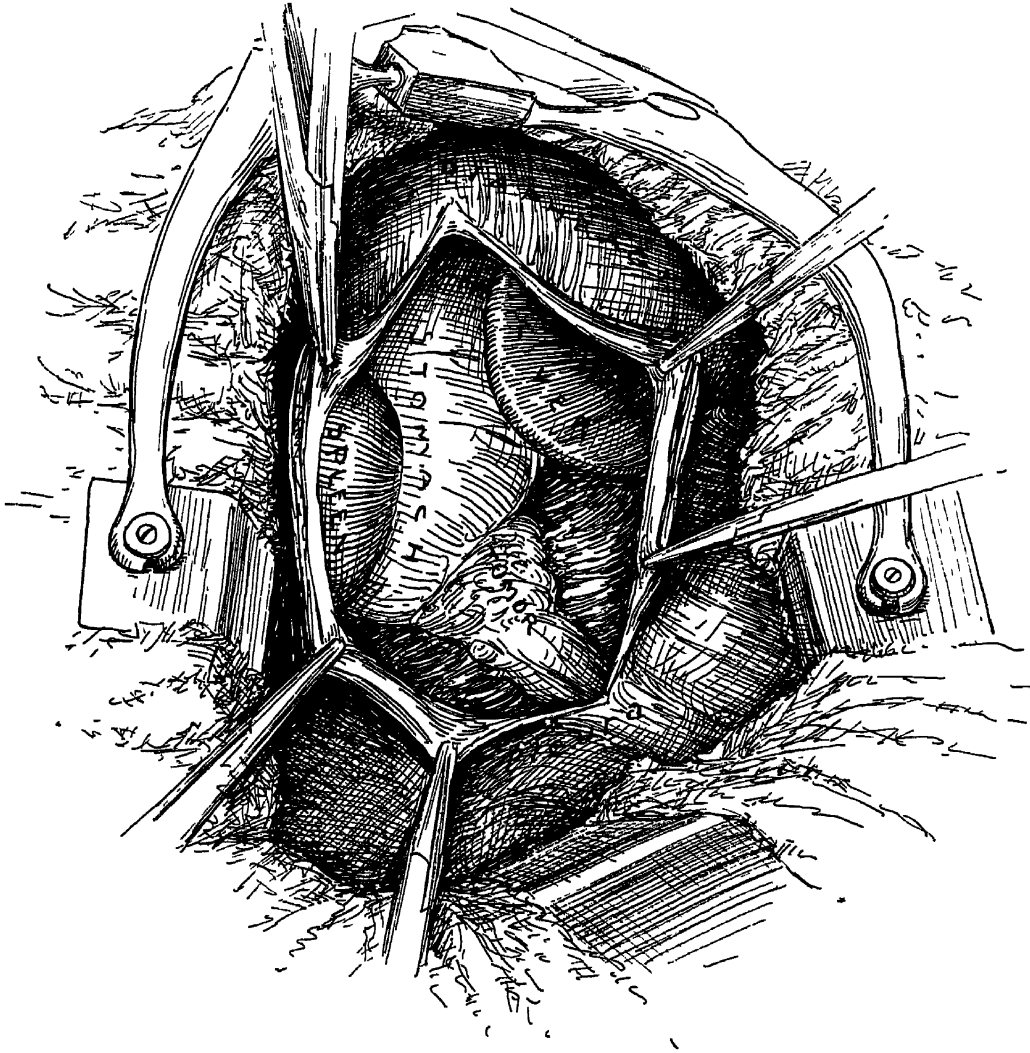


Fig 4—Carcinoma of esophagus, lower third. Parietal pleura excised exposing esophagus and tumor. Diaphragm opened radially in line of its muscle fibers showing relationship of esophageal tumor to stomach and to liver and spleen. (Lahey and Marshall: Am. J. Digest. Dis.)

*sounds*, is resorted to *ad infinitum*. As soon as a noticeable dilatation has been forced, the dilatation from pharyngo-esophageal entrance with sounds is undertaken and continued until a maximal expansion is obtained. This returns the function of deglutition to the normal

supported on the basis of his very numerous successful experiences. Only in the most unusually exceptional cases 1 of the complicated operative methods was found to be necessary. Martin had very fortunate results with dilatation treatment.

**Unusual Gastroenterological Surgical Problems**—Some complicated gastroenterologic problems with which Lahey and Marshall<sup>16</sup> have had to deal are discussed and plans which they employed in their management are presented. These include a 2-stage plan employed in the management of a *large gastrojejunal fistula* (Figs. 1 and 2);

centage of successful results and because of lowered operative risk. It is unnecessary to point out that such highly technical surgical procedures require not only considerable experience and technical ability on the part of the surgeon, but also the collaboration of a skilled internist in the selection of cases. Boldness and skill must be tempered by

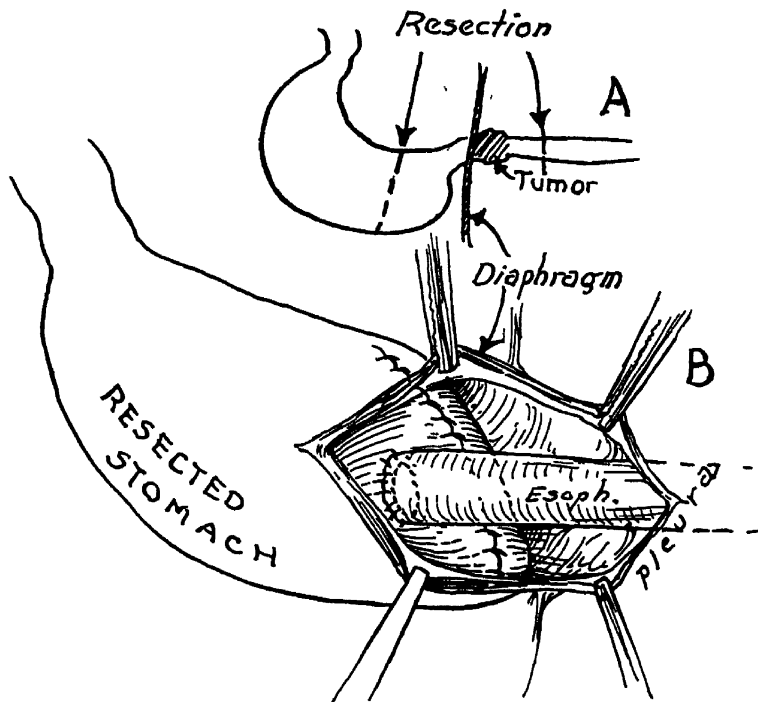


Fig 5—Carcinoma of esophagus, lower third. A, Illustrating portion of stomach and esophagus containing tumor to be resected. Divided end of stomach has been inverted. Esophageal stump has been transplanted into anterior wall of stomach re-establishing continuity of esophagus with stomach. Stomach is brought partly into thoracic cavity to bridge gap caused by removal of portion of esophagus. Rent in diaphragm is closed about the stomach. (Lahey and Marshall. Am J Digest Dis.)

experiences with *transpleural resection of the lower end of the esophagus for malignancy with restoration of swallowing* (Figs. 3, 4 and 5); the management of *duodenal diverticula* (Fig. 6), and a plan for successfully restoring the fecal stream in *high jejunal resection* with a short jejunal stump.

The authors point out that these highly technical operations designed for such problems have become justifiable because of an increasingly high per-

centage of successful results and because of lowered operative risk. It is unnecessary to point out that such highly technical surgical procedures require not only considerable experience and technical ability on the part of the surgeon, but also the collaboration of a skilled internist in the selection of cases. Boldness and skill must be tempered by

sound judgment on the part of both internist and surgeon and results must certainly justify the selection of cases. Rash surgery can hope only to discredit both and cannot be condemned too vigorously.

The value of *preliminary loop colostomy* in the correction of *gastrojejunocolic fistula* is described by Pfeiffer and Kent.<sup>17</sup> The authors perform a loop colostomy preliminary to correction of gastrojejunocolic fistula which re-

sults in cessation of symptoms and return of the patients to a normal physical state, thus greatly reducing the operative risk. Complete disappearance occurred of intraperitoneal inflammatory reaction involving the jejunum, colon, their mesenteries and the adjacent peritoneum. In 2 instances ulcerations themselves disappeared. Colonic contamination

and Fallis.<sup>18</sup> The mortality of subtotal gastrectomy for peptic ulcer in the authors' clinic for 15-year period was 10 per cent, and for the past 5 years 5 per cent. In the last consecutive 53 cases there was but 1 death. The most important factor in this falling mortality has been the increasing experience of the operators, which resulted in several

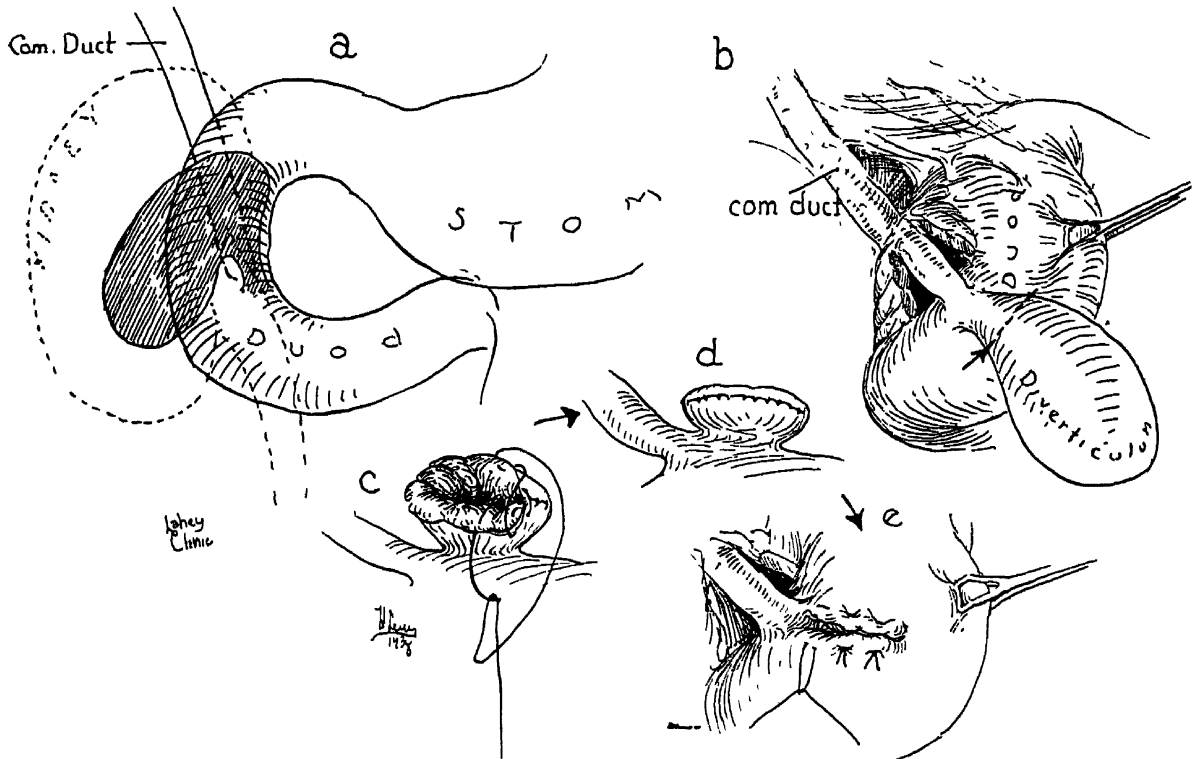


Fig 6—Diverticulum of duodenum. Operation for removal. *a*, Relationship of diverticulum to duodenum, common bile-duct and kidney is shown *b*, Duodenum has been mobilized, common bile-duct and head of pancreas exposed. Diverticulum has been freed from surrounding structures. *c* and *d*, Diverticulum has been removed. Neck of sac has been closed by inverting sutures of catgut, reinforced with mattress sutures of silk. (Lahey and Marshall. Am J. Digest Dis.)

was avoided and adequate protection of the repaired transverse colon was secured, thus abolishing the danger of leakage and peritonitis. The disastrous general and local results of gastrojejuno-colic fistula are in a large part due to reflux from the colon into the upper digestive tract and not from loss of gastric contents into the colon as hitherto suggested.

Certain technical problems in *partial gastrectomy* are considered by McClure

improvements in technic. Important points in *preoperative preparation* are care that the *hemoglobin* is at least **70 per cent**; attention to *dental prophylaxis*; *refusal to operate within 6 weeks of an upper respiratory infection*; repeated *lavage of the stomach with sodium bicarbonate solution* in the 2 days before operation; final preoperative *lavage with half-strength hexyl-chlorometa-cresol* (200 cc. being left in the stomach);

and repeated *enemas* to cleanse the colon. The anesthetic of choice is *spinal nupercaine* administered by the Jones method. Sedation is accomplished by means of *seconal* (3 grains—0.2 Gm) and *morphine sulfate* ( $\frac{1}{4}$  grain—0.016 Gm.). Blood-pressure is maintained by the administration of 600 cc.

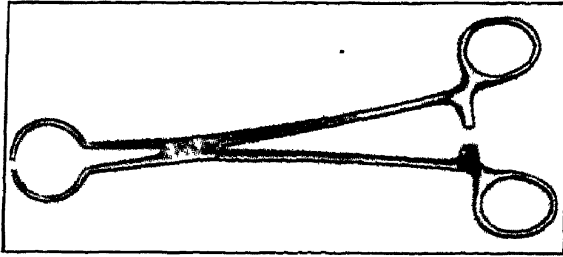


Fig 7—Ring clamp for applying traction to duodenum. (McClure and Fallis Ann Surg)

of 10-per-cent *glucose* followed by 600 cc. of *citrate blood*. A midline incision is used.

The duodenum is mobilized, after cutting the right gastric artery, with the aid of a special ring clamp (Fig. 7), which encircles the prepyloric area as a retractor. It is sectioned distal to the ulcer if this is possible without encroachment on the common bile-duct or the papulla of Vater. If this is not possible, as may occasionally be ascertained only after opening of the duodenum, the section is made through the ulcer or proximal to it, as circumstances indicate. Closure of the duodenal stump is then made with the aid of a modified Furniss clamp (Fig. 8), which is furnished with a detachable handle and is easily manageable in a deep wound. A purse-string suture, interrupted Lembert sutures, and omental reinforcement complete the closure.

From two-thirds to three-quarters of the stomach should be removed. The left gastric artery is ligated near its origin and the stomach divided between 2 crushing Payr clamps, the proximal clamp having a wing-nut on its tip to prevent

slipping. The Hofmeister-Finsterer type of anastomosis is preferred, which brings the jejunum through a rent as far posteriorly as possible in the transverse mesocolon. The part of the cut end of the stomach other than the anastomotic site is closed by a double layer of continuous stitches, and an additional row of interrupted Lembert sutures. Precautions to be taken are the use of guy sutures to avoid kinking or rotation of the jejunum, the insertion of the posterior continuous suture well toward the mesenteric border of the jejunum so that sufficient jejunal wall is left for the remainder of the sutures, and the accurate closure of the rent in the mesocolon around the stomach or the 2 arms of the jejunum, as the case may be. Important structures of which damage should be avoided are the common bile-duct and the middle colic artery. Drainage is used only in cases of injury to the pancreas or when there is uneasiness about the integrity of the duodenal closure.

Important points in *postoperative care* are *continuous gastric suction* for 4

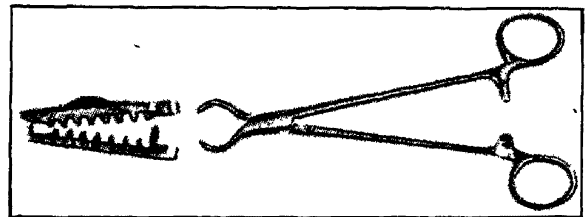


Fig 8—Modified Furniss clamp with its detachable handle (McClure and Fallis Ann Surg)

days, with only sips of water or ice allowed by mouth and a subsequent conservative attitude with regard to increasing the diet. *Alkaline powders* and *amphogel* are given regularly post-operatively.

**Motor Function of Stomach After Resection**—A clinical and roentgenographic study of 74 patients subjected to



gastrectomy for various conditions was made by Vitkin<sup>19</sup> to determine the status of their gastric motor functions. The gastric resections had been performed by the Billroth II method or some modification thereof.

From these observations, the author arrived at the following conclusions:

(a) As a rule, the stomach resected by the Billroth II method shows a rhythmic

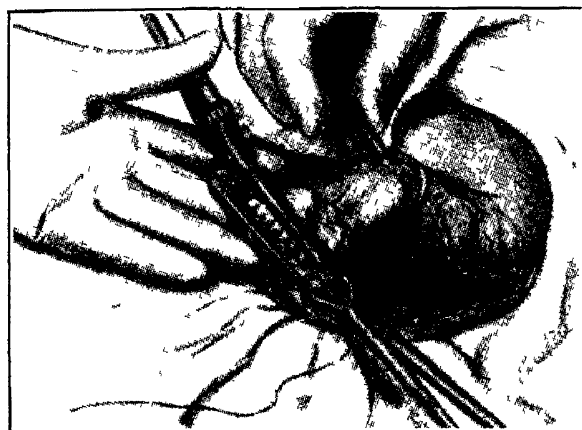


Fig 9—Duodenum just before sectioning. McClure modification of Furniss clamp shown in place, with ring clamp just proximal to pylorus (McClure and Fallis. Ann Surg.)

mic evacuation. This type of evacuation is observed both on resection by the classic method of Billroth II or by its Hacker-Eiselsberg or Kronlein-Reichel modifications.

(b) In order to obtain rhythmic evacuation from a stomach resected by the Billroth II method, there is no need to complicate this operation by further modification, *e g*, the operation by Finsterer, Bal, Goetze, or others.

(c) The type of evacuation obtained does not depend upon the extent of the resected region, the rhythmicity of evacuation is observed on subtotal gastrectomy.

(d) There is no difference between the types of evacuation obtained in stomachs resected by the Billroth I and in those resected by the Billroth II method.

TABLE I  
DISTRIBUTION ACCORDING TO DIAGNOSIS

<i>Diagnosis</i>	<i>No of cases</i>
Cancer of antrum	9
Cancer of body of stomach	12
Ulcer of antrum	6
Pyloric ulcer	4
Ulcer on lesser curvature in region of angle	18
Ulcer on lesser curvature above angle	14
Duodenal ulcer	2
Peptic ulcer	8
Gunshot wound of stomach*	1
Total	74

\* The patient with the gunshot wound was operated upon 18 years previously, but for the past 2 years had been under the author's observation.

(e) At present there are no data which would substantiate the belief in the formation of a sphincter in the anastomosis region after gastrectomy. Following resection by the Billroth II method, such a formation was considered to be quite impossible.

(f) The periodic closing and opening again of the anastomosis are explained in the main by peristaltic contractions and distentions of the efferent intestinal loop nearest the anastomosis.

(g) Gastric tone after a partial gastrectomy becomes normal in time, a hypotonic or atonic stomach becomes normal in tone.

(h) Spasms of the anastomosis after gastrectomy undertaken for cancer present an early symptom of recurrence of the cancer in the region of the anastomosis.

(i) After gastrectomy, most patients exhibit hyperplastic gastritis, though without any subjective manifestations.

(j) After gastrectomy, chronic jejunitis follows, also without clinical manifestations.

(k) Normal evacuation of the stomach resected by the Billroth II method or by its Hacker-Eiselsberg modification is in complete accord with the general condition of good health, which gradually improves with the passing years.

**Gastrosopic Observations After Operations on Stomach**—Moersch and Walters<sup>20</sup> review gastrosopic observations on 100 patients who had undergone operations on the stomach and who subsequently developed gastric distress. They concluded that gastrosopy can be of assistance in reaching a better understanding of the factors leading to gastric distress after operations on the stomach.

Contrary to the commonly accepted teaching that gastritis is found in all stomachs after operation, in 30 per cent of these cases of persistent dyspepsia gastrosopic evidence of disease was not present. As a rule, in the cases in which abnormality of the gastric mucosa was not demonstrated by gastrosopy the functional factor was found to be rather pronounced, and most patients responded symptomatically to therapeutic measures directed to this end. The diagnosis of gastritis was made on gastrosopic observations in 56 cases. In contrast to the cases in which gastrosopy revealed normal gastric mucosa, the response to medical management was not as satisfactory, and further operation was frequently required.

*Postoperative gastritis* may be thought to be a manifestation of gastritis that existed before operation. This is often true, and many postoperative complications might be avoided if this possibility is always recognized before operation. On the other hand, it is known that gastritis which is present before operation may disappear after operation. That gastritis undoubtedly does develop after operation is seen from the fact that evidence of gastritis was present in 56 per cent of

the cases in this study. In comparison, Swalm, Jackson and Morrison found gastritis in only 35 per cent of their routine gastrosopic examinations and Schindler reported an incidence of 41.8 per cent.

Speculating about the possible factors responsible for postoperative gastritis, the authors suggest that no doubt in many cases a pre-existing gastritis is the responsible factor. In their opinion a poorly-placed stoma with inadequate drainage of the stomach is an important factor. Gastritis is not as likely to develop if the stoma retains an activity resembling that of a sphincter. Infection constitutes an important exciting factor. Other lesions, such as gastrojejunal ulcer, carcinoma, gastric ulcer and benign tumor, can and do develop in the stomach after operation, and gastrosopy may be of assistance in their recognition. In 5 cases in this series, carcinoma of the stomach was found on gastrosopic examination and in 6 cases gastrojejunal ulcer was visualized.

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gastrectomy for various conditions was made by Vitkin<sup>19</sup> to determine the status of their gastric motor functions. The gastric resections had been performed by the Billroth II method or some modification thereof.

From these observations, the author arrived at the following conclusions:

(a) As a rule, the stomach resected by the Billroth II method shows a rhythmic

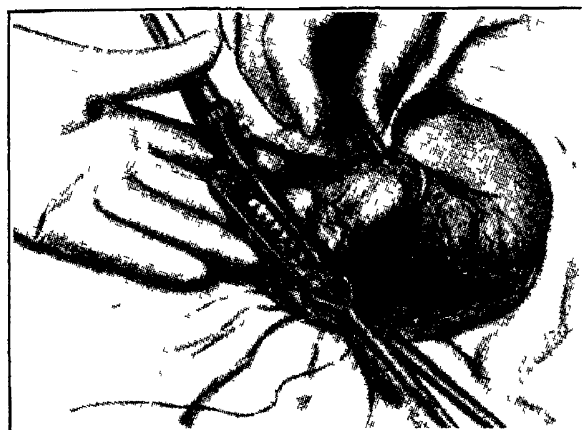


Fig 9—Duodenum just before sectioning McClure modification of Furniss clamp shown in place, with ring clamp just proximal to pylorus (McClure and Fallis Ann Surg)

mic evacuation. This type of evacuation is observed both on resection by the classic method of Billroth II or by its Hacker-Eiselsberg or Kronlein-Reichel modifications.

(b) In order to obtain rhythmic evacuation from a stomach resected by the Billroth II method, there is no need to complicate this operation by further modification, *e g*, the operation by Finsterer, Bal, Goetze, or others.

(c) The type of evacuation obtained does not depend upon the extent of the resected region, the rhythmicity of evacuation is observed on subtotal gastrectomy.

(d) There is no difference between the types of evacuation obtained in stomachs resected by the Billroth I and in those resected by the Billroth II method.

TABLE I  
DISTRIBUTION ACCORDING TO DIAGNOSIS

<i>Diagnosis</i>	<i>No of cases</i>
Cancer of antrum	9
Cancer of body of stomach	12
Ulcer of antrum	6
Pyloric ulcer	4
Ulcer on lesser curvature in region of angle	18
Ulcer on lesser curvature above angle	14
Duodenal ulcer	2
Peptic ulcer	8
Gunshot wound of stomach*	1
Total	74

\* The patient with the gunshot wound was operated upon 18 years previously, but for the past 2 years had been under the author's observation.

(e) At present there are no data which would substantiate the belief in the formation of a sphincter in the anastomosis region after gastrectomy. Following resection by the Billroth II method, such a formation was considered to be quite impossible.

(f) The periodic closing and opening again of the anastomosis are explained in the main by peristaltic contractions and distentions of the efferent intestinal loop nearest the anastomosis.

(g) Gastric tone after a partial gastrectomy becomes normal in time, a hypotonic or atonic stomach becomes normal in tone.

(h) Spasms of the anastomosis after gastrectomy undertaken for cancer present an early symptom of recurrence of the cancer in the region of the anastomosis.

(i) After gastrectomy, most patients exhibit hyperplastic gastritis, though without any subjective manifestations.

(j) After gastrectomy, chronic jejunitis follows, also without clinical manifestations.

tions only under rare circumstances. Of more importance in the causation of postoperative wound and respiratory complications is the air-content of pathogenic germs.

Culturing 10 cubic feet of air throughout an operating day, MacDonald found the total number of nonpathogenic and pathogenic microorganisms to be 230 494. Of this total, 0 02 were found to be beta hemolytic streptococci, 0 556, alpha hemolytic streptococci; and 3 49, hemolytic streptococci, making a total of 4 066 different types of hemolytic streptococci which could cause complications in individuals whose general and local resistance was below par.

Further studies of the bacteriological content of the circulating air of operating rooms will undoubtedly aid in eventually increasing our knowledge of why clean operative wounds, protected by proper skin antisepsis, wound drapes, proper ligatures, etc., still continue to be unexpectedly infected.

**Sterilization by Ultraviolet Radiation**—Kraissl, Cimiotti and Meleney<sup>3</sup> summarize 4 years of experimental and clinical experience with ultraviolet radiation in the operative field. In their estimation the unsterile air in the operating room is an important source of wound contamination and practically can be eliminated by the use of ultraviolet radiation. This can be accomplished without injury to tissue if the proper spectrum and intensity are adhered to and controlled.

### Amputations

**Life Expectancy After Amputation**—In as much as the majority of amputations are performed upon the lower extremities of elderly arteriosclerotic or pre-elderly diabetic individuals, military and industrial surgeons will be greatly interested in the data

which Zur Verth<sup>4</sup> has compiled regarding amputations in younger, healthy persons.

Zur Verth, a Hamburg orthopedist, has upset the view largely entertained that amputated individuals do not live as long as persons possessed of all their limbs. His conclusions demand respect inasmuch as they are based upon observations regarding 60,000 living and 3600 dead individuals who have suffered amputations of various parts.

Most of the amputations were performed between the ages of 19 and 44 years. Zur Verth collected data to show the number of those amputated who were dead 13 years later and compared these data with the normal mortality rate at each given age (19 to 44). The results were surprising. The mortality rate of the amputated, computed for each age level, was 3 68 per cent as compared with the mortality rate of 5 98 per cent for the remainder of the male population.

The same results were obtained from observations on all those amputated during the World War and not confined to the age levels of 19 to 44. Accordingly, the life span of those amputated is more favorable at all age levels than that of the general population.

These statistics cause the Reviewer to wonder whether or not the lifespan of any amputated individual is not sociologically prolonged by the fact that such individuals, following their individual amputations (and regardless of cause), subsequently lead a sheltered, well-fed and quiescent life.

**Painful Stumps—Treatment**—Reporting on 74 patients with painful amputated stumps, Shiosberg<sup>5</sup> gives his results in treating such patients with subcutaneous injections of  $\frac{1}{8}$  grain (0.01 Gm.) of synthetic *vitamin B*. Eleven patients were completely relieved (15 per cent), 39 showed con-

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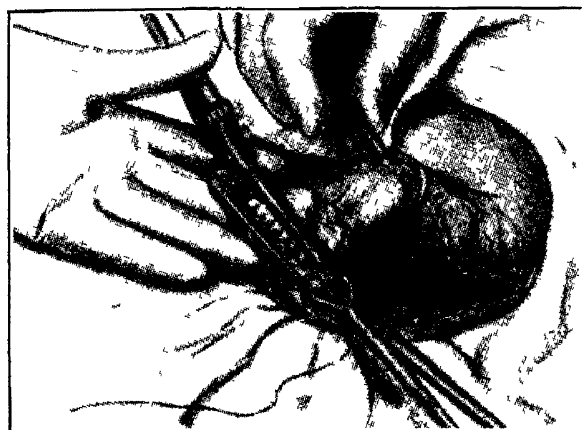


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**Treatment**—Greenwald has shown that in severe burns the adrenals are damaged and hypoglycemia results. Pöhlmann<sup>7</sup> points out that protoplasmic shock causes an increased permeability of the capillaries. This latter condition, he states, can be corrected by the administration of adrenal cortex extract and vitamin C. Since Greenwald has demonstrated that the adrenals are definitely affected by severe burns in experimental animals, it would seem logical to conclude that the use of adrenal cortex extract in severe burns would be a valuable supplementary form of treatment in combatting protoplasmic shock and also lighten the burden on the damaged adrenals, thus aiding in their restoration to normal activity.

The observations of Pöhlmann and of Greenwald suggest that the future treatment of severe burn cases might be improved materially by further experimental work on animals, by a careful study of the adrenals and of blood sugar levels in fatal cases which have come to autopsy and by clinical trials of **adrenal cortex extract**, **vitamin C** and **glucose intravenously** in future cases where clinically there is evidence of adrenal damage.

### Controlled Fluid Therapy

It is essential to consider the history and clinical picture presented by the patient in addition to the hematocrit, specific gravity, and plasma protein determinations for the interpretation of the state of dehydration in order to institute rational fluid therapy, according to Drew, Scudder and Papps.<sup>8</sup> In simple dehydration due either to lack of fluid intake, diarrhea, excessive sweating, severe vomiting, or shock of psychogenic, traumatic, or postoperative origin, which is uncomplicated by hemorrhage, there is a definite rise in the cell volume, the

specific gravity of the whole blood and of the plasma and the protein percentage of plasma. Treatment for the first 3 of these conditions consists in administering fluids until these elevated values tend to approach the normal.

In the treatment of *shock*, measures directed to overcome the severe arteriolar and venular spasm as well as the capillary paralysis and dilatation and a great loss of circulating blood volume must be instituted. The use of **hypertonic sodium chloride** is especially effective in relieving the arteriolar spasm, in decreasing the viscosity of the blood and aiding the return of fluid from the tissues into the circulation. The use of **adrenal cortex extract**, or **eschatin**, has proven helpful in restoring capillary tone, raising the blood-pressure and redistributing electrolytes. **Blood transfusions** are given in order to maintain the gain initiated by sodium chloride and adrenal cortex extract.

In the presence of *hemorrhage* there is an immediate fall in the specific gravity of the whole blood and a drop in the cell volume, as shown by the hematocrit. The changes in the specific gravity of the plasma are less well defined. Treatment of this condition consists of restoring the blood volume by repeated **transfusions**. It is absolutely essential to ascertain whether the shock is complicated by hemorrhage. When there is not only loss of fluid but also loss of protein, a tendency for the hematocrit curve to rise while the protein value continues to fall has been noted. In these cases marked degrees of hemoconcentration and shock must be neutralized by sufficient use of **fluids**, although the previously diminished protein concentration should not be reduced to the edema level.

When *acute changes* take place, as noted in chronic disease in which anemia

is present and probably hypoproteinemia, any of the ordinary blood tests—the red cell count, the hemoglobin or hematocrit determination—will not evaluate true hydration. It is necessary that a combination of all be used, particularly the specific gravity of the plasma. The treatment consists in reducing the protein values to approximately normal levels with the restoration of cellular contents of the blood. With a gradually falling protein level impending, edema may be suspected. For the patient who is severely ill and who may not be able to utilize fluids until the severe spasm of the peripheral vessels is relieved, the procedure is to determine the degree of hemoconcentration or anemia and that of dehydration or edema and resort to the proper therapy according to the indications present. Progress should be determined by repeated studies of the blood and the degree of dehydration. Hourly determinations should be made if necessary.

### Diabetes

**Mortality**—Surgeons should note the reported increased mortality in diabetes throughout the United States, and especially in Pennsylvania, for its consequent bearing on surgical results.

Strome and Blaine<sup>9</sup> have recently analyzed the trend in mortality from diabetes in Pennsylvania and in the United States Registration Area. Many factors must be considered in comparing American data with that from other countries and even data in this country accumulated in recent years in contrast to past decades. Allowing for these factors, however, it would appear that diabetes mellitus is increasing in this country and so is the mortality.

According to Strome and Blaine, it would appear that: (1) Diabetes mortality rates are higher in the United

States than in any other civilized country. (2) Pennsylvania leads the United States with the highest mortality rates in the United States Registration Area. (3) Mortality rates from diabetes are increasing every year. From 1906 to 1937 the mortality rate in the United States Registration Area increased 186 per cent, whereas in Pennsylvania it increased 297 per cent. Death rates from all causes both in the United States Registration Area and in Pennsylvania steadily declined during the same period.

It is interesting to note that since insulin therapy was inaugurated, there has been a marked lowering of mortality in individuals below the age of 45 but an increased mortality above that period. As Dublin once remarked, insulin does not confer immortality, these patients sooner or later succumb to the degenerative diseases of their age, such as pneumonia, cancer, arteriosclerosis, and nephritis.

**Diabetic Gangrene — Treatment**—Meleney<sup>10</sup> reports favorably on the control of infected lesions in diabetics by the local use of fresh solutions of *zinc peroxide*. Zinc peroxide markedly inhibits the growth of the hemolytic streptococci and all anaerobic bacteria, including the organisms causing gas gangrene and the anaerobic streptococci. It neutralizes or inactivates the toxins formed by these organisms and does not inhibit the development of granulation tissue or the reparative process.

Zinc peroxide, as a white powder, should be suspended in sterile distilled water in proportions to make a free flowing cream and then applied to every part of the wound surface. Gauze soaked in the same material should then be placed over the area and a layer of vaseline gauze to prevent evaporation. Dressings should be changed daily.

## Air Embolism Following Perirenal Insufflation

**Prevention**—Commenting on Weyrauch's report of a death following perirenal insufflation of air for diagnosing adrenal tumors, Mencher<sup>11</sup> states that in his experience, which consists of 80 perirenal insufflations, there was never any untoward complication. Granting that the needle is passed properly and that no blood is aspirated, the writer believes that the most important safeguard in the procedure of insufflation is dependent on the type of delivery system employed. He has never used any other system than a 2-bottle pneumothorax machine which delivers air under gravity pressure at about an 8-inch level. With this type of system the gas flows under relatively low pressure, at least a pressure low enough so that if the needle should be within the kidney substance or within abdominal musculature there will be no flow of the gas. If the needle is within the perirenal space, gas will "bubble" through the inverted infusion drip apparatus. The easy bubbling of gas has been an excellent guide and indicates that the proper plane has been reached. When equilibrium is established between the pressure of gas in the perirenal space and the 8-inch pressure from the machine, gas no longer flows. Respiratory excursions are transmitted to the "bubble chamber" at this point. The amount of gas instilled varies in individuals and has been anywhere from 250 to 900 cc.

Mencher further notes that perirenal insufflation is not indicated in cases of renal tumors, since pyelographic studies should be sufficient to make a diagnosis.

## Arterial Embolism

**Treatment**—Koucky and his associates<sup>12</sup> report their experiences in 25 cases of peripheral arterial embolism.

They found that most of these cases occur in *late adult life*. Two of the 25 patients were less than 10 years of age and 2 were between 70 and 80 years. As is usually observed, *mitral heart disease*, on the basis of *subacute bacterial or chronic rheumatic carditis*, was the direct etiologic agent. The lower extremities were more frequently involved than the upper. In the present series the ratio was 5:20.



Fig 1—Tube and flanges bent forward for introduction into pleural cavity. (Leahy: Jour Am Med Assoc.)

The treatment of arterial embolism is divided into 4 types: nonoperative, arteriotomy, arterectomy and amputation. An embolism to the upper extremity can usually be treated conservatively because the collateral circulation will furnish sufficient blood to the limb. In the experience of the authors, embolism of any large vessel in the lower extremity down to and including the popliteal arteries is a surgical emergency and should be treated as such without any hopeful procrastination. The time factor in the performance of an *embolectomy* is of great importance and once the site of the embolus is reasonably certain, there should be no delay. It is important to remember that with procrastination, reformation of a thrombus at the site at which the embolus has impinged becomes an added risk to embolectomy and makes further operations necessary, thus increasing mortality. If a free flow of



blood after the embolus is removed is impossible, it is best to remove a segment of the artery (*arterectomy*), thus removing the irritable focus of the vasospastic reflex and facilitating collateral circulation.

The authors are of the opinion that the usual case follows a more or less typical course toward a fatal termination and that this course can be altered. The

shock, infection and death. The authors found that in cases in which *amputation* was done as soon as improvement was apparent the results were better. This is borne out by their figures which showed that the average duration of life of 3 patients following embolectomy was 39 hours; of 4 of the 6 following amputation, 47 days; and of 14 of the 16 given conservative treatment, 20 days, a

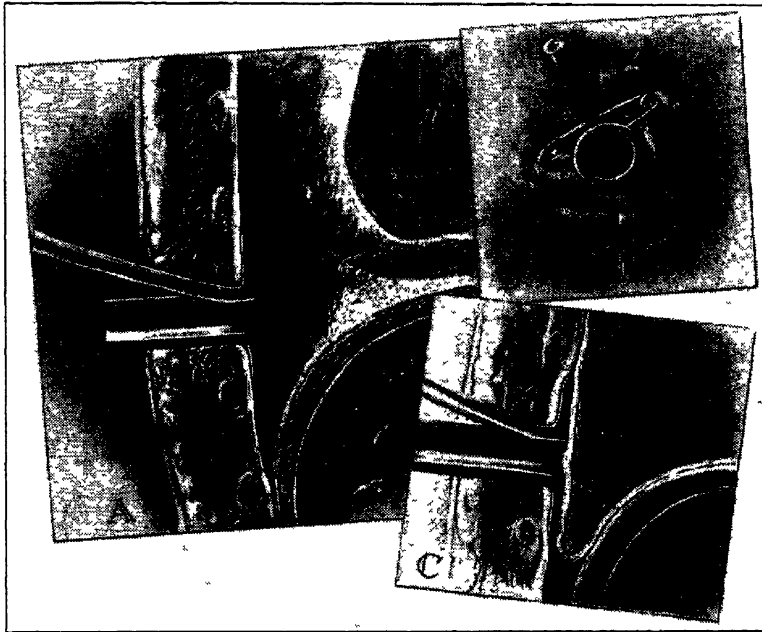


Fig. 2—A, Cross section showing tube in position with relationship of inner end to parietal pleura. B, Appearance of outer end with pin in place and wound closed. C, Cross section showing tube in position following re-expansion of lung (Leahy. Jour Am Med Assoc)

patient is usually brought to the hospital in poor general condition, conservative methods are employed, and he seems to rally and appears in a much better condition. Meanwhile, the extremity becomes *gangrenous*. As the patient improves, he is kept on this conservative management for days or even weeks, still appearing constantly to improve. Then there is a general increase in the toxemia. The fever rises, the pulse accelerates and a moderate leukocytosis gives evidence of toxemia. As this increases, the emergency guillotine amputation is performed. This is followed by

respective mortality rate of 100, 66 and 88 per cent.

### Empyema

**Open Treatment**—Leahy<sup>18</sup> advocates a new type of drainage tube in the treatment of empyema thoracis by the *open thoracotomy method*. Surgeons are divided in their opinions regarding the merits of the "open" and the "closed" type of drainage in empyema thoracis. Regardless of which type of treatment is used, experienced surgeons admit that the ordinary straight, stiff, and eyeletted drainage tube is fre-

quently unsatisfactory in the treatment of patients who have thick or "clabbery" drainage. Certainly, thick or clabbery drainage material mitigates against a speedy recovery. Leahy advocates a flanged, double-barrelled drainage tube (Fig. 1) which provides for secondary irrigation independent of the main portion through which drainage takes place. A very good feature about Leahy's new type of tubes is that the flanged portion permits the lung to expand completely without interference or damage from a tube projecting into the pleural cavity (Fig. 2).

### Surgical Erysipelas

**Treatment**—On the basis of 85 cases of facial erysipelas, Rantz and Keefer<sup>14</sup> conclude that the administration of *sulfanilamide* markedly shortens the duration of the illness if given within 72 hours of its onset. They studied, without special selection, patients admitted to the male wards of the Boston City Hospital with a diagnosis of facial erysipelas from October, 1937, to June, 1939. As a control, they reviewed the records of 43 similar patients admitted during 1936 and 1937 before the use of sulfanilamide was instituted. All received a standard therapy consisting of *bed rest, fluids, sedatives* and *cold magnesium sulfate compresses* on the affected areas. Forty-two patients, in the recent group, were given *sulfanilamide* in addition to the usual treatment given the 43 control cases. These received as a routine  $1\frac{1}{2}$  to 2 drams (6 or 8 Gm.) by mouth in the first 24 hours, with a maintenance dose of from  $\frac{3}{4}$  to  $1\frac{1}{4}$  dram (3 to 5 Gm.) a day thereafter. As criteria for the evaluation of the effect of the drug, the authors considered the duration of fever, the incidence of complications and the mortality.

If the time of institution of the sulfanilamide therapy is considered in relation to the onset of the disease, it is found that of 21 patients treated on or before the third day of illness, the total febrile course averaged 5.2 days, with an average of 3.0 days after beginning the drug. In cases in which the drug was given after the third day, fever persisted for an average of 9.1 days and subsided in an average of 4.2 days after the onset of medication. The total duration of fever, therefore, was markedly shortened in patients treated on or before the third day of the illness. Their studies further showed that it has little effect after this interval. Complications occur frequently in the treated cases, but less often in those treated early.

### Gas Gangrene

**Treatment by Combined Use of Sulfanilamide and Serum**—Because of the various claims regarding the usefulness of sulfanilamide in treating gas gangrene, Singer<sup>15</sup> investigated the protective power of sulfanilamides combined with antitoxic serum against experimental *Clostridium welchii* and *Clostridium septicum* infections. In a number of mice infected with soil suspensions and given a sufficient amount of the drug to cure an infection produced with pure culture of *Clostridium welchii*, post-mortem studies revealed *Clostridium welchii*. Infection was produced by injecting subcutaneously into the tissues of the back 24-hour cultures of the particular anaerobe. The antitoxic serum was injected 2 hours after infection and immediately after the first dose of the drug. The views of Stephenson and Ross that infections with strongly toxigenic strains were less responsive to chemotherapy were not substantiated, as strain S 107, the most toxic strain, was the most susceptible to treatment. Tests

with *Clostridium histolyticum* showed that sulfanilamides were completely inactive against it. The different sulfanilamides were about equally effective against infections with *Clostridium welchii* S 107 and with *Clostridium septicum*.

Only sulfanilamide and sulfapyridine were tested in conjunction with serum therapy. The amount of antitoxic serum administered was by itself inadequate to inhibit the course of the infection. Infections with multiples of 1 fatal dose were cured with relatively small quantities of drug combined with an amount of serum that by itself would be quite ineffective. This suggests that a similar form of therapy might be of considerable value in treating gas gangrene infections in the human being. The action of sulfanilamide drugs on *Clostridium septicum* infections was much weaker than on those of *Clostridium welchii*. However, much better results were obtained with the combined treatment. It seems that the better results with sulfanilamides plus serum treatment of *Clostridium septicum* infections are due, at least partly, to a kind of double action of the sulfanilamides on *Clostridium septicum*, while in *Clostridium welchii* infections the action of the drug limits itself to bacteriostatic and growth inhibiting effects. Some other mechanism not investigated in these experiments may be concerned. An attempt to treat fatal *Clostridium oedematiens* infections with a combination of drug and serum failed, as did treatment with drugs alone.

As surgeons are so well aware, gas gangrene is seldom found to be, clinically, the result of a single organism such as *Clostridium welchii*, *Clostridium oedematiens*, etc. As a rule, there are other organisms such as *Staphylococcus aureus*, streptococci, etc., which, it is believed, makes gas gangrene infections worse because of a symbiotic action re-

sulting from the "mixed infection." On this basis, it would seem well to use sulfanilamide (in conjunction with gas gangrene serum) for the deleterious effect it might exert on the secondary invading microorganisms which would not be affected by the administration of specific gangrene serum.

### Spontaneous Gangrene and Trophic Ulcers

**Vishnevskiy Treatment**—Shnaper<sup>16</sup> reports 15 cases of spontaneous gangrene of the extremities, 12 cases with trophic ulcers, 2 cases with circulatory disturbances due to chilblain, and 1 case due to a snake bite. The patients with spontaneous gangrene complained of excruciating pain in the extremity, intermittent claudication, coolness and cyanosis of the extremity with the development of gangrene of the toes or the entire extremity. The patients had been previously submitted to a number of medical and surgical procedures without success. The treatment consisted of a circular **procaine hydrochloride block** according to the method developed by Vishnevskiy. From 200 to 225 cc. of a 0.25 per cent of procaine hydrochloride solution was slowly injected into the skin and subcutaneous tissue and below the aponeurosis in a circular fashion above the lesion. This procedure was followed by a mild rise in temperature, normal sleep and disappearance of pain within the first 24 hours. The pain returned after this period but was much less intense and disappeared gradually in from 2 to 5 days. The affected extremity became warmer and a line of demarcation rapidly developed in cases exhibiting beginning gangrene of toes or fingers. In some of the cases the circular block was supplemented within 3 weeks by a **lumbar block** (injection of from 75 to 100 cc. of procaine hydrochloride

solution into the right or left lumbar region). The favorable effect was observed for periods of from 1½ to 2 years.

This form of treatment was developed by Vishnevskiy and is based on Speranskiy's theory that local irritation involves the central nervous system with the resulting upset in the normal internervous relations. He proposed the method of treating trophic lesions by interrupting the conduction of painful reflexes.

While the treatment is new and therefore unproven, it seems well worth a trial in the treatment of these conditions which seldom respond, or do so slowly, to past accepted forms of therapy.

### Hypertension

#### Section of Splanchnic Nerves —

Davis and Barker<sup>17</sup> report that section of the splanchnic nerves of hypertensive patients makes them more responsive to medical treatment with *potassium thiocyanate*. They find that the majority of hypertensive patients observed by them respond favorably to the administration of potassium thiocyanate as evidenced by a drop in the systolic and diastolic blood-pressures and a fall in the blood cholesterol, total proteins and hematocrit reading. Headache, insomnia, nervousness, fatigue, dyspnea and heart consciousness are relieved, and an actual decrease in the size of the heart occurs. There is a small group of patients, however, who are resistant to thiocyanate therapy. In this group of patients the drug must be pushed to the toxic level before any effect can be obtained, and the lack of a safe margin makes it impossible to control symptoms or blood-pressure successfully. It is to be noted that in their experience with these patients, bilateral supradiaphragmatic section of the splanchnic nerves alone has failed to decrease their blood-pressure or to cause a fall in the chemi-

cal constituents of the blood. After operation the authors noticed, however, that 4 patients responded to the administration of thiocyanate. The blood-pressure, systolic and diastolic, has shown a definite drop and there has been a decided improvement in the condition of the patients. The authors believe that section of the splanchnic nerves has in some unknown manner increased the sensitivity of a small number of patients to thiocyanates. The observations of Davis and Barker will serve to aid those hypertensive patients who in the past have been relegated to permanent bed rest following the failure of surgical intervention to lower their blood-pressure or otherwise ameliorate their symptoms.

### Irradiation Sickness

**Treatment**—The use of *thiamin chloride* therapy was studied by Immler and Wammock<sup>18</sup> for the control of severe symptoms of radiation sickness in 21 patients.

These observers found that daily injections of 3000 international units, in the majority of the patients, gave prompt and complete relief. When there was a recurrence of the symptoms an increase in the dosage of the thiamin chloride was necessary.

One patient receiving Roentgen therapy on the left aspect of the neck required 4500 I.U. hypodermically to control the recurrent nausea while another required 10,000 I.U. to eliminate the nausea and vomiting. The hypodermic administration of thiamin chloride is definitely superior to the oral route. This presents a problem in the treatment of outpatients. These patients lose confidence in the medication and may refuse to follow the course of radiation treatment. The solution of this problem requires the patient to return to the hos-

pital for daily hypodermic administration of vitamin B<sub>1</sub>.

It is preferable to give small doses daily rather than massive doses every second day. It might be possible to find a direct relationship between the actual level of vitamin B<sub>1</sub> and the onset of radiation sickness if daily or twice daily estimations of the vitamin B<sub>1</sub> content in the blood serum could be made.

### Ludwig's Angina

**Surgical Management** — Reviewing the mortality of Ludwig's angina in 5 Boston hospitals, Williams<sup>19</sup> found that it averaged 54 per cent. Such a rate suggests that the disease does not receive proper recognition and treatment. In Ludwig's angina a massive swelling, often bilateral, always brawny and tender but rarely fluctuant, involves the suprahyoid region, being extreme in the submaxillary area. The overlying skin is conspicuously free of inflammation, showing only edema. The floor of the mouth is raised, edematous and brawny. The mucous membrane beneath the tongue is often ulcerated and dirty grayish white. The tongue is swollen and pushed upward, and it may become so crowded by sublingual edema that its tip protrudes between the teeth. Respiratory obstruction, due to blockage of the airways by an elevated or edematous tongue, is frequent.

Emergency tracheotomy is often necessary in this condition and had to be performed on 8 (25 per cent) of the 31 patients studied. Four patients on whom tracheotomy was not done died of asphyxia. Bronchopneumonia complicated 8 cases, 7 of which terminated fatally.

The essential points in treatment are to establish an airway, to relieve tension, to secure drainage and to combat the infection through supplementary meas-

ures. **Tracheotomy** is the most dependable means of securing an adequate airway. The choice of anesthesia warrants deliberation. **Pentothal** was used in 4 and **evipal** in 2 cases. Its use must be restricted to those familiar with the administration of pentothal. **Sulfanilamide** is of great value in cases showing positive *Streptococcus hemolyticus* cultures. **Zinc peroxide** is indicated when anaerobic organisms are present.

In addition to the above measures, appropriate **incisions** and **drainages**, when and where indicated, should be made as well, using **radiotherapy** if recommended by the radiologist in consultation.

### Aluminum Acetate and Parathyroid Surgery

The theory that parathyroid solution exerts its primary effect on the phosphorus metabolism rather than on the control of the blood calcium level has been investigated by Helfet.<sup>20</sup> According to this theory, (1) solution of parathyroid controls the inorganic phosphate level of the blood; (2) it prevents this level from rising to a point which would disturb any metabolic process in which the phosphates are concerned; (3) an accumulation of phosphate in the blood acts as a stimulus to increase the solution of parathyroid; (4) solution of parathyroid produces phosphate control by stimulating the excretion of phosphate by the kidney and furthermore by mobilizing calcium ions from the storehouse in the bones; (5) if the parathyroid glands are removed from the body, it will not be able to utilize the blood phosphate.

On the basis of this theory it would appear important to remove the stimulus to the overproduction of solution of parathyroid in the body and thus reduce the absorption of phosphorus. This plan

should be helpful in the treatment of *diseases of the bones* and also in *rheumatoid arthritis*.

A method for reducing the absorption of phosphorus consisted in giving daily an amount of *aluminum acetate* with a phosphate-combining power equivalent to from 150 to 220 mg. of calcium. A correspondingly smaller dose was given to children. In order to have the aluminum combine with the phosphate of all the food eaten during the day, one-quarter of the daily dose was taken after each meal. It should be noted that an excessive amount of aluminum acetate should be avoided, since it may predispose to the production of rickets. In the patients studied with this form of therapy, no other treatment was resorted to. The patients were given their normal diets. Not less than 1 pint of milk was taken daily as a source of calcium and vitamin D.

In 3 of the 4 cases of *generalized fibrocystic osteitis* definite improvement was noted. This suggests that the phosphorus radical is responsible for the overstimulation of the parathyroid gland.

In 12 cases of *rheumatoid arthritis* and 3 of *spondylitis ankylopoietica* the results of *aluminum acetate* therapy were most promising. A number of the patients had previously received gold therapy or had some septic focus removed without any effect. Twelve of the 15 patients showed improvement in general appearance, 10 gained weight, 9 were definitely relieved of joint pains. Two of the patients showed no improvement. The relief of symptoms in some of the patients was dramatic and most of them improved except for joints which were ankylosed before treatment was started. Two of the patients who had previously experienced typical deformities of the fingers were able to correct the deformities after 4 months

of treatment. Some of the spindle-shaped swellings of the finger joints disappeared. Although no *physical therapeutic measures* were utilized in these patients, nevertheless, such form of therapy, under careful supervision, should enhance the aluminum acetate form of treatment.

Eight patients afflicted with *Paget's disease* improved in appearance and gained in weight. They were able to walk further and accomplish more work before experiencing fatigue. There was less pain in the bones and joints and in some cases the distress disappeared entirely. Roentgenograms of 2 cases showed some change towards normal contour of the bony outline.

On the basis of this new theory and the results obtained in early experiments, Helfet believes that this new line of treatment should be further investigated for the relief of these distressing conditions which heretofore have not responded satisfactorily to any form of therapy.

### Pilonidal Sinus

**Ambulatory Surgical Treatment—**According to Rogers,<sup>21</sup> the failures in the treatment of pilonidal sinus at the Massachusetts General Hospital have been reduced from about 30 per cent to around 3 per cent since 1932, when a special study of this disease was undertaken. Analysis showed that 30 per cent of 119 patients treated during the 8 preceding years had not been cured of their disease. Investigations led to the conclusion that *large radical excisions are unnecessary* and that the problem is chiefly one of wound healing in the presence of infection. In 1935 the conservative excision of pilonidal sinuses was begun in the outpatient department. The tissues were locally infiltrated with *procaine hydrochloride containing epinephrine*, and the sinus tract and

hair nest were dissected out through a midline skin incision in a nearly bloodless field by means of a small cautery blade. The resultant narrow wound was then packed with gauze and the patient was allowed to go home. In most cases this proved to be a minor procedure requiring from 20 to 30 minutes and causing the patient no more reaction than does the excision of a wen. The occasional patient with a lesion complicated by extensive scarring was best managed in the hospital under a general anesthetic. Of 150 *cautery excisions* done between 1935 and 1937, 14 were done in the hospital and 136 in the outpatient department. All the wounds were left open because the natural way for infected wounds to heal is by second intention. Except for certain cases of definitely delayed healing, the average time was about 9 weeks. The wounds healed to a soft, inconspicuous linear scar.

Surgeons generally will be interested in the fact that the author is convinced that most failures are not due to incomplete excision of diseased tissue but to faulty wound healing caused by *infection and retained dead space*, that there is no practical or theoretical justification for the radical excision of large blocks of normal skin and subcutaneous tissue, and that in unselected cases the highest percentage of cures can be obtained by conservative excision of the sinus tract and hair nest under direct vision, followed by solid second intention healing of the open wound, with the patient ambulatory and under the care of the same surgeon from first to last.

Inasmuch as 97 per cent of these patients remained cured for from 1 to 4 years with *conservative excision and ambulatory care*, such results must be regarded as superior to those obtained by ordinary methods. Moreover, such

treatment materially reduces hospital costs and beds when it is remembered that most cases of pilonidal sinus occupy a bed for 7 to 10 days and infected cases much longer.

### Pulmonary Abscess

**Treatment**—Because of the beneficial results of using diluted alcohol ( $\frac{2}{3}$  to 1 ounce—20 to 30 cc.—of a 10 per cent solution of ethyl alcohol in normal saline) intravenously in mild pulmonary suppurations, Mazel<sup>22</sup> was encouraged to use *alcohol by the rectal route* in treating pulmonary abscesses. He believed that the alcohol would be absorbed by the inferior hemorrhoidal vein and thus gain direct access to the pulmonary circulation without passing through the liver. The alcohol apparently exerts a bactericidal effect on the early suppurative focus in the lung, supposedly stimulates the reticuloendothelial tissue to the formation of antibodies and assists in obliteration of the formed cavity. The method consisted of a daily preliminary cleansing enema followed in from 2 to 3 hours by introduction into the rectum of from 2 to 2½ ounces (60 to 75 cc.) of 10 per cent ethyl alcohol in physiologic solution of sodium chloride. The average duration of treatment was from 30 to 35 days. After some 20 enemas the temperature, as a rule, fell, the sputum diminished in amount and lost its offensive odor. With further therapy, infiltration and cavities disappeared in roentgenograms. The author concludes that the rectal method is as effective as the intravenous. The method is most effective in the stage of suppurative infiltration before the formation of a cavity. It is effective in the acute and subacute stage but is of no value in the chronic stage.

The use of *alcohol by proctoclysis*, so that the liver will be shortcircuited

and its effects be exerted quickly, directly and undiminished upon the pulmonary tissues, is a novel form of treatment the results of which are unproven as yet, but deserves future interest and consideration.

### **Skin-grafting Complicated by Transplantation of Fibrosarcoma**

While unusual, autogenous transplantation of malignancy must be considered in performing surgery on cancer patients, Harrell and Valk<sup>23</sup> reported such an instance in a patient who had a chronic ulcer of the right heel and on whom a full-thickness pedicle graft from the left thigh was performed. A fibrosarcoma at the base (thigh) of the pedicle developed. The right leg was amputated and the ulcerated area of the thigh was excised. Both specimens proved, microscopically, to be fibrosarcoma.

### **Surgical Geriatrics**

Surgeons dealing with elderly patients who often heal poorly will grow more and more interested in blood protein determinations. Because of the complexity of the available methods for the determination of the proteins of the blood, the widespread use of this important laboratory procedure has been neglected.

Shuman and Jeghers<sup>24</sup> tried the Kagan method for the determination of the blood proteins combining simplicity and quantitative accuracy.

Three hundred and twenty patients were studied on the Fifth Medical Service of the Boston City Hospital; 25 individuals were used as controls. The blood sample was collected at the same time as for the Hinton test. Two cubic centimeters were placed in a small dry test tube and centrifuged until the serum separated from the clot. The serum and proteinometer remained at room tem-

perature for 10 minutes before using. By means of a calibrated pipet, 0.015 cc. (15 cmm.) of serum was introduced into the glass cylinder of the proteinometer. The time required for the drop of serum to fall 10 cm. through the oil was measured to one-tenth of a second, using a stopwatch. The protein value of this serum was determined from a calibrated chart. A correction was made for the temperature of the oil.

Most of these determinations required less than 1 minute to perform. In 238 cases (74.5 per cent), the total protein values were in normal range from 6 to 8 Gm. per 100 cc. Approximately 25 per cent of all the patients showed subnormal values for the blood protein. In the low protein group edema was definitely more common. On this basis it appeared reasonable to consider hypoproteinemia as the main, or at least, an important contributory cause of the edema.

The difficulty of controlling cardiac decompensation in the presence of hypoproteinemia is important and frequently overlooked.

Whenever edema is present, the level of the blood proteins should be ascertained immediately. The effect of dehydration on the level of the blood protein is important. As a rule, seriously ill patients are dehydrated when brought into the hospital, thus causing an apparent increase in the total protein value of the blood. Until the fluid balance of the body has been restored to normal, it is impossible to obtain a true estimate of the blood protein level.

The determination of the total blood protein value is important as a test for detecting a dietary deficiency. The majority of patients with *hypoproteinemia* will respond promptly and favorably to *dietary measures* alone. In the presence of liver disease or gastrointestinal



disturbance reducing the efficiency of absorption and utilization of the food, dietary measures may not prove sufficient. For these cases it may be necessary to resort to intravenous therapy using *blood transfusion* or *injection of lyophile serum*. Future developments in this field may offer some form of amino-acids for intravenous use.

### Thrombophlebitis of Leg

**Diagnosis**—A frequent source of pulmonary embolism is that due to bland, nonobstructing thrombosis of the leg which may occur in active life or with the patient quiet in bed. The thrombotic process may be limited to the venous plexuses among the muscles below the knee or it may involve the femoral or iliac veins. While ordinarily difficult to identify, this type of thrombosis often can be diagnosed whether or not embolism has occurred, if the combination of clinical symptoms with discomfort in the posterior part of the knee on forced dorsiflexion of the foot is kept in mind.

**Treatment**—While, as a rule, *conservative treatment* for this condition is indicated when *embolism* has occurred or whenever symptoms and signs have appeared at least once, Homans<sup>25</sup> advises *exploration* and *division of the femoral vein*. *Exploration and division of the femoral and iliac veins* likewise may be the indicated procedure for the cure of *peripheral vasospasm*, more particularly if the vein has been the seat of previous thrombophlebitis. Exploration may also be advisable to guard against further recurrence of pulmonary embolism.

Homans believes that *division of the superficial femoral vein* in the presence of a *bland, nonobstructing thrombosis below the knee* is rapidly curative and is followed by no swelling and cyanosis of the limb. Division of the

common femoral and profunda veins, however, for a bland, nonobstructive thrombosis that occupies the femoral vein itself causes considerable edema and cyanosis. *Division of the superficial, common femoral, or common iliac vein* subsequent to an old canalized thrombophlebitis, produces very little disturbance and may give relief of reflex vasospasm and by the prevention of backflow, produce definite benefit to the venous circulation.

### Ulcers of Leg

**Treatment**—Believing that the majority of leg ulcers are associated with diseases of the veins, Zimmerman and Faller<sup>26</sup> regard such ulcers as essentially infectious in origin and develop on the basis of periphlebitic infiltration and cicatrization. They are similar in pathogenesis and clinical manifestations and respond to similar forms of therapy. The essential predisposing pathologic change is ischemia from inflammatory sclerosis of the skin and subcutaneous tissues. External secondary infection adds to the fibrosis and circulatory insufficiency. The tissue changes are permanent and irreversible and the ulcers may persist or continue to evolve even after the associated varicosities are completely eradicated.

From the various therapies for crural ulcers, 1 fact survives: *gentle, mechanical pressure*. Mechanical measures have been the mainstay of the authors' therapy for ulcers and eczemas of venous origin and are relied on almost to the exclusion of all other forms of treatment. They do not regard the treatment of this condition as a difficult problem. It is almost invariably ambulant; bed rest and elevation are rarely found necessary. The patients are permitted to go about their usual affairs without restriction as long as the pressure bandages

are in place. Frequently healing of ulcers by ambulant treatment has been accomplished when prolonged bed rest had failed. Recumbent management is limited to the small group of patients who do not tolerate occlusive dressings and to those with acute infection severe enough to demand bed rest.

For obtaining gentle elastic pressure, *Unna's paste boot* is relied on not only for the treatment of ulcers but also for other complications of varicose veins, including local phlebitis, phlebitic indurations and varicose eczemas. Occasionally if in long standing, callous ulcers, after the usual initial rapid improvement, the tempo slows down, renewed stimulus may be obtained by *strapping the ulcer with strips of adhesive tape and by applying the boot over the strapping*. If this stimulus also wears off before the ulcer is healed, further acceleration may be secured by applying *pads of rubber sponge under the boot*. At first the boots are changed once a week; later, when edema has subsided and the amount of exudate has diminished, they may be left on for 2 or 3 weeks or longer. Patients are instructed to return with boots on. They are removed in the clinic, the limbs are cleansed and the new boot is applied. When healing is complete, further protection with Unna's paste or elastic bandages for several weeks longer is advised until the scar is sufficiently firm and tough.

In addition to the above local treatment, *varicosities* requiring *ligation* or *injection* are also given appropriate attention.

### Chronic Burrowing Ulcers

**Treatment**—One of the most difficult and discouraging superficial lesions surgeons are called upon to treat is the undermining, burrowing ulcer caused by

the micro-aerophilic type of *Streptococcus hemolyticus*. Meleney, who has contributed toward this subject probably more than any other writer, has tested many chemicals for combating this condition. He and Harvey<sup>27</sup> believe that the ideal treatment for chronic undermining, burrowing ulcers is as follows: When a patient with such a lesion comes to the hospital, after careful anaerobic and aerobic bacteriologic studies, *zinc peroxide* powder suspended in sterile distilled water in the consistency of a 40 per cent *cream* should be applied to the wound, care being taken to use effective material, to get contact and to prevent evaporation. It is important that this dressing should be removed daily. At the same time, *sulfanilamide* should be administered by mouth, 18 grains (1.2 Gm.) every 4 to 6 hours. If the patient tolerates the medication, and jaundice, destruction of leukocytes and erythrocytes, fever or delirium does not ensue, sulfanilamide should be continued. If toxic symptoms supervene, sulfanilamide should be discontinued. If after 1 week there are any areas of activity, an operative procedure is required to expose undermined areas so that they can come in contact with the cream. To date, Meleney's zinc peroxide cream has benefited these lesions more than any previous form of treatment.

### Wound Healing

**Effects of Different Types of Suture Materials**—Since the early days of surgery, recurring controversies have arisen relative to the merits of a particular type of suture material. Various surgeons are "wedded" to a particular type of suture material and apparently in their hands they achieve better results than do their confreres with the same material. This, like the use of a certain

instrument, is due to the manner in which it is handled by the surgeon.

Meade and Ochsner<sup>28</sup> studied, accordingly, the tensile strengths of catgut, silk, linen and cotton, and the tissue reaction and wound healing caused by each. *Catgut* was demonstrated to be (1) a strong suture before being placed in tissue; (2) absorbed at a variable rate depending upon its size, the chemicals present and the reaction of the individual; (3) a possible source of allergic reactions; (4) a deterrent in wound healing; (5) unreliable when knotted under tension unless triple or quadruple throws knots are tied; and (6) above all, a possible cause of wound infection. *Nonabsorbable suture* materials produce no allergic reactions, allow rapid wound healing and reliable square knots can be tied. *Silk* and *linen* show early decrease in tensile strength as compared to *cotton*. *Cotton* and *linen*, as products of the field, may contain spore-forming anaerobic pathogens. *Silk* contains the ordinary pyogens, but anaerobic organisms were not found. Chemically-treated silk and catgut are proteins; the former, being non-absorbable, excites much less tissue reaction. Sinuses may develop in wounds sutured with silk in the presence of infection and they will not heal until the suture is removed or expelled. *Cotton*, in the presence of infection, is less likely to cause sinuses. Cotton is proposed as a pliable, easily sterilized, nonirritating, inexpensive suture of sufficient strength in the recommended sizes for most surgical procedures. It has been used in 91 surgical procedures, primary healing having taken place in 88.

*Catgut*, by producing the most reaction and slowest healing, was graded 4, linen 3, silk 2, and cotton, producing the least reaction and earliest healing, 1.

It would have been interesting if a comparison of the relative value of *alloy-wire*, as developed by Babcock, of Philadelphia, had also been made. The latter material has been used extensively in the Philadelphia area for several years by many surgeons and has been found to be an ideal material for selected areas and cases. Alloy-wire can be used in the presence of infection with apparently little or no "foreign body reaction." The Reviewer prefers it as the suture material of choice and necessity in *laparotomies on malignant patients* whose operative wounds not infrequently rupture all too easily through faulty healing due to hypoproteinemia and hypovitaminosis. With the use of alloy-wire, *elderly patients* who have been operated upon for a *strangulated femoral or inguinal hernia*, can be placed in a wheel chair the following morning and on subsequent convalescent days, thus obviating that "fatal friend of the aged"—so-called hypostatic pneumonia.

**Vitamin C and Wound Healing—**Delayed wound healing and disruption of operative wounds have long been noted in patients suffering from malnutrition and chronic wasting conditions which result in hypoproteinemia and a hypovitaminosis. Bartlett, Jones and Ryan<sup>29</sup> have studied this subject thoroughly. They report the vitamin C content of the blood plasma of 13 normal subjects and of 188 preoperative patients. The 13 central subjects showed a blood plasma content varying from 0.77 to 1.62 mg. per 100 cc. with an average of 1.42 mg. Of the 188 preoperative patients on whom fasting determinations were made, the average blood plasma level was 0.43 mg. per 100 cc. with a variation from zero to 1.89 mg. As a concentration below 0.5 mg. per 100 cc. was obtained in 126 of the patients, this may be considered defi-

nitely abnormal with respect to their vitamin C metabolism. A consistent fall in the plasma vitamin C was noted postoperatively, especially in those patients who had had extensive operations performed. *Fruit juices* and *ascorbic acid* is indicated preoperatively and postoperatively in patients who have a low plasma vitamin C level.

### POSTOPERATIVE COMPLICATIONS

#### Early Postoperative Feeding—

Those surgeons who advocate an immediate return to a normal diet, postoperatively, will be interested in the observations of Halperin,<sup>30</sup> who employed early postoperative feeding in 65 unselected cases excluding, however, cases in which operations had been performed on the stomach or the biliary tract. The types of diets given were carbohydrate (cooked cereals, jello, custards, hard candy, toast and synthetic fruit juices), protein (gelatin, beef stock, soups, soft boiled eggs and lean meats), carbohydrate and protein and control diets (liquids for 48 hours and then a soft diet).

Approximately 25 per cent of the 23 patients given the *protein diet* vomited almost immediately after its ingestion. This, the author believes, was *psychic* and due to the fact that the diet was *not palatable*. Most of the patients had to be forced to eat and many complained bitterly that they had no desire to eat such food. The average time postoperatively at which this diet was given was 10.8 hours. About one-half of these patients had mild gas pains before eating, and approximately 44 per cent experienced some form of transitory gas pain after eating. Flatus by rectum was observed 27 hours postoperatively. Five

of the group had spontaneous bowel movements, eliminating the necessity of routine enemas. Eleven patients were given a *carbohydrate diet* about 9 hours postoperatively. Two had mild gas pains before eating and 4 had slight gas pains after eating. No patient in this group had distention. Routine enemas were given 48 hours postoperatively. One of these patients vomited after eating. The average postoperative time at which 20 patients were given the *combined protein and carbohydrate diet* was 12 hours. Nine of this group experienced gas pains prior to eating. Four had gas pains after taking the diet. None of the patients had distention. Flatus was noticed on an average of 25 hours postoperatively. Two had spontaneous bowel movements. Enemas were administered at approximately 48 hours postoperatively. The 11 patients given the *control diet* experienced, at some time or other during the 48 hours, gas pains varying in intensity. At the end of 48 hours they were placed on the usual soft diet. The average patient in this group began to pass flatus at the end of 45 hours. There were no cases of distention.

Halperin's observations undoubtedly agree with those of many other surgeons who advocate early "solid foods" excepting in cases of resection, anastomosis, or obstruction, which after all constitute but a small per cent of operations.

In this connection, it is generally agreed that a type of case which gives the least postoperative abdominal distention, gas pains, etc., is the so-called "street emergency case"—the type of case which is brought in off the street and immediately operated upon without any preliminary emptying of the gastrointestinal tract.

Halperin concludes that early postoperative feeding is practical and obviously efficacious in combatting postoperative gas pains and distention. Gas pains occur less often and peristalsis is re-established earlier, as evidenced by the fact that patients begin to pass flatus sooner. The type of diet administered is important. It should be of semisolid consistency and should not contain foods that might produce reflex nausea. Fats should be excluded in the early postoperative diet, since they tend to slow up peristalsis and inhibit to some degree the digestion of carbohydrates. With the exception of orange juice and milk, carbohydrate foods such as toast, cooked cereals, gruels, hard boiled eggs, gelatins, custards and mashed potatoes make up an ideal postoperative diet.

**Postoperative Blood Chlorides—**The studies of Bekerman<sup>31</sup> show that an estimation of the blood chlorides preoperatively of certain types of cases can aid in their postoperative management. He studied the blood chloride levels of 115 surgical patients. The chloride content of the patients in the preoperative period as expressed in milligrams per 100 cc. of sodium chloride varied within considerable limits from 425 to 590 mg., the figure in women being somewhat higher than in men. A fall in the blood chlorides was a *constant sign of gastrointestinal obstruction*. It is not, however, pathognomonic of obstruction, since it may be present in diseases characterized by profuse vomiting or diarrhea, in pneumonia and in peritonitis. A fall in chlorides was constantly observed both in mechanical and in dynamic obstruction of any segment of the intestine. As was to be expected, the degree of the fall depended on the duration of obstruction. A uniform fall of from 10 to 30 mg. was noted on the postoperative day. This did not appear to depend on the

anesthesia or on the character or duration of the operative intervention.

The author considers a postoperative fall of more than 30 mg. as indicative of a threatening complication, intestinal atony or pneumonia. It is interesting to note that a parallelism was observed between the extent of lowering of the blood chlorides and the gravity of symptoms of intoxication. A fall in the chloride level of 150 mg. as compared with the preoperative level, or a level below 300, signifies a grave state threatening the life of the patient. It is recommended that repeated infusions of *hypertonic solution of sodium chloride* and *blood transfusion* be given in the *preoperative period* as a prophylaxis against postoperative complications in patients with a lowered preoperative blood chloride level.

**Pulmonary Embolism and Thrombosis—**In an interesting examination into postoperative complications, Culp<sup>32</sup> analyzes 88 cases of pulmonary embolism encountered at the Brady Urological Institute during the past 20 years. There were 32 cases of fatal embolism proved at necropsy, 11 of presumptive fatal embolism in which necropsy was lacking, 21 of pulmonary infarcts from which the patients recovered, 4 infected pulmonary infarcts recognized at necropsy and 20 cases with incidental pulmonary infarcts discovered at necropsy. The majority of the 32 cases of proved fatal pulmonary embolism occurred in private patients more than 60 years of age, after operations performed under spinal anesthesia. Continuous intravenous infusions appeared to be a factor in producing thrombosis in the lower extremities in 4 instances. It is surprising to learn that in only 18.8 per cent was the thrombosis recognized clinically. Any untimely activity seemed to be capable of dislodging thrombi. Analyses of the

11 cases of presumptive fatal pulmonary embolism revealed essentially the same contributing and the same nonessential factors as did the foregoing cases. The majority of the 21 nonfatal pulmonary infarcts occurred during the past 10 years in private patients more than 60 years of age given spinal anesthesia. Continuous intravenous infusion was directly responsible for 2 cases. Only 23.8 per cent of the patients presented clinical evidence of thrombosis. The 4 patients with fatal infected pulmonary infarcts after perineal prostatectomy performed under caudal anesthesia were undernourished and more than 60 years of age.

This survey but indicates anew that spinal anesthesia is not as safe as many claim. From observations in a large eastern hospital, the Reviewer (Wright) has noted that continuous spinal anesthesia causes the highest number of pulmonary complications.

All the patients had a clinical course simulating pneumonia. Thrombosis of the leg was diagnosed clinically in only 1 case and was proved at necropsy in 2. Thrombosis of the lower extremity was observed clinically in 5 cases and demonstrated in the leg at necropsy in 6, and in the pelvic veins in 4; in 10, the source of the embolus was not demonstrated at necropsy.

The following *prophylactic measures* are recommended: (1) Continuous intravenous infusion should not be used unless absolutely necessary. (2) Every effort should be made to prevent peripheral venous stasis by adequate treatment of associated circulatory disease, fall in blood-pressure, postoperative abdominal distention and by the elimination of unnecessary pressure on peripheral vessels due to strapping and the like. (3) Wound infections should be minimized by careful aseptic operative

technic and mild bacteriostatic agents. ***Drainage of postoperative abscesses*** should be established immediately. (4) The greatest need is the recognition of thrombosis in the lower extremity. The legs should be measured on admission, before operation and before patients get out of bed. (5) Untimely activity should be avoided in the presence of thrombosis. Absolute ***bed rest*** is the most conservative and most practical treatment for thrombosis and prevention of embolism. In view of spinal anesthesia factors, one wonders if it might not be well to add: "Except in certain selected cases, ***open drop ether anesthesia*** is still the safest anesthesia."

**Thrombosis — Prophylaxis** — It is interesting to note that according to Bergquist,<sup>33</sup> prophylaxis against postoperative thromboses can be promoted by a ***daily analysis of the blood coagulation time*** before and after the operation and by the regular ***determination of the thrombocytic count***. Employing Kristenson's pipet for the latter and Petré's procedure for the former (normal coagulation level from 3 to 5 minutes) and administering ***heparin*** when needed, the author was able to avoid thrombotic or embolic complications in 50 cases so controlled. In 8 of these cases heparin was deemed necessary. While the failure for thrombosis to occur in only 50 postoperative cases is no criteria for adopting his methods, some of his observations are important in that he verified the observation that, whereas thrombocytes did not increase appreciably, the blood coagulation time had a tendency to fall below the lowest normal level (3 minutes) between the fifth and the eighth day and occasionally as late as the tenth. Whenever this tendency occurred he administered intravenously 0.6 cc. of a 5 per cent solution of heparin. He re-

tested after 4 hours. If a subnormal tendency continued, he injected an additional 1 cc. A retest was made after 6 hours and 2 cc. administered, if necessary. The test was repeated 7 or 8 hours later.

The author holds the generally accepted view of the etiology of thrombosis (modification in the blood stream, biochemical changes in the composition of the blood, possible endothelial lesions) but believes that vortex formations in the circulation in postoperative cases cause a prethrombotic condition, which however can be controlled and guarded against by daily blood coagulation tests. He does not believe that the coagulation time needs to be elevated to 3 or 4 times the normal level in order to insure prophylaxis, but has come to the belief that a 1-minute drop may constitute in individual cases an idiopathic danger signal of a prethrombotic condition even if the minimum 3-minute level has not been reached.

**Aspiration Pneumonia** — With a view to decreasing the incidence of postoperative aspiration pneumonia, Flagg<sup>34</sup> observes that E. M. Hawks has suggested that the lithotomy position, by causing increased intra-abdominal pressure, the stomach being compressed between the fundus and the diaphragm, increases the likelihood of regurgitation of gastric contents. Intra-abdominal manipulation, in which the operator's hand is swept over the fundus of the uterus, may also cause pressure against the stomach.

The author states that it is the opinion of a nose and throat associate that it is not possible to give enough barbiturate to abolish the gag reflex. While this is very likely true as an isolated fact, the addition of a small degree of general anesthesia or, what is more frequent, the addition of anoxia will

promptly subdue the glottic reflex, permitting unembarrassed aspiration.

According to Flagg, there is no doubt that *continuous suction* should be available wherever unconscious patients are cared for. Apparatus is not enough; a test should indicate at least 15-pounds suction, instantly available. Premedication reduces the cough reflex and increases the ease of aspiration as well as the difficulty of expulsion of aspirated material.

Aspiration is increased by carbon dioxide.

**Spinal Anesthesia Complications—Headache and Vomiting**—Analyzing the anesthetic complications in 500 operations in which spinal anesthesia had been used, Jennings and Karabin<sup>35</sup> found that 153 patients (30.6 per cent) suffered from postanesthetic headache; the headaches of 67 patients (43 per cent of headaches) were considered as severe, while 86 patients (56 per cent) suffered moderate headaches. The onset occurred within 24 hours in 143 patients and after 24 hours in 10 patients. Ninety per cent of the patients were given less than 1½ grains (100 mg.) of procaine hydrochloride; the remaining 10 per cent received 1½ grains (100 mg.) or more. Of the first group, 29.6 per cent developed headaches, whereas only 10 per cent receiving the larger doses were afflicted. One patient developed a severe headache which was almost continuous for 7 days and recurred frequently for 8 months. A neurological examination revealed no obvious cause for the headaches. Nausea and vomiting developed in 34.6 per cent of the patients. The best treatment for postspinal anesthetic headache, in the authors' estimation, is *prolongation of the "flat in bed" period*. Such headaches occur more often than is commonly realized and their incidence

seems to be inversely proportional to the time of recumbency.

[The Reviewer has noted a higher incidence of postspinal anesthetic headaches in patients where the anesthesia was administered by inexperienced internes or residents who found it necessary to make a number of punctures before obtaining a free, bloodless flow of spinal fluid. Naturally, multiple punctures make for a greater and prolonged leakage of spinal fluid. A single puncture with a small caliber needle in the fifth lumbar space followed by the "flat position" for 24 hours should make for a minimal incidence of headaches.]

#### Postoperative Causes of Death—

Analyzing the cause of 1265 postoperative deaths occurring in 24,816 surgical operations, Petrén<sup>36</sup> found that 53 per cent occurred from the basic disorder, the basic injury or a complication peculiar to the disorder or injury, and 21 per cent from a pulmonary complication, most often pneumonia or pulmonary embolism. The incidence found by him of pulmonary complications in the elderly group is confirmatory of general surgical experience. Of the patients with fatal pneumonia, 86 per cent were 55 or over, almost half were 70 or over, and 68 per cent of those with pulmonary embolism were aged 60 years or over. In the remaining 26 per cent death was due either to wrong or to questionable indication for operation, with some of the patients for various reasons too weak for the operation performed, or to a technically faulty operation or to some special postoperative complication, not pulmonary.

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# NEUROSURGERY

Edited by ROBERT A. GROFF, M.D.

## SURGERY OF THE HEAD

By C. S. DRAYER, A.B., M.D.

**General Considerations**—Vazquez<sup>1</sup> has described an ingenious device for securing hemostasis of the scalp. This consists of a triangular needle 7.5 cm. long which can be passed between the scalp and the skull after infiltration of the skin with local anesthetic. A flat piece of spring steel articulates with the ends of the needle in such a way that adjustable pressure is exerted on the scalp. Once a series of these instruments has been placed about the operative site, an incision down to the bone may be made with 1 stroke of the scalpel, and little or no bleeding is said to occur.

tion than when a large body electrode is used, and there is no shrinkage of vessels. The instrument controls bleeding even when the tips of the forceps are immersed in saline.

**Diagnosis** — *Electroencephalograms* are proving to be valuable adjuncts in the localization of lesions near the surface of the cerebrum. In 43 such cases, Yeager and his associates<sup>3</sup> found the electroencephalogram was 86 per cent accurate. In only 2 instances was the electroencephalogram actually misleading, and in some cases this examination was more accurate than any other employed.

ACCURACY OF DIAGNOSIS AND LOCALIZATION OF INTRACRANIAL LESIONS  
MADE BY VARIOUS METHODS

Method	Total	Accurate	Missed	Doubtful
Electroenceph . . . .	43	37 (86.0%)	4 (9.3%)	2 ( 4.7%)
Clinical	43	35 (81.4%)	2 (4.6%)	6 (14.0%)
Pneumoenceph.	17	14 (82.3%)	1 (5.9%)	2 (11.8%)
Surgical	38	36 (94.7%)	2 (5.3%)	0

Vasquez has also been using a high speed motor craniotome with fine teeth, so designed that they throw bone dust in the diploe and thus produce reasonably good hemostasis at the bone edge. A "skate" is attached to protect the dura from the cutting edges.

For single bleeding points, Greenwood<sup>2</sup> has designed special forceps with insulation between the 2 blades. These 2 blades are used as the electrodes between which the coagulating current can pass. In this way the amount of tissue through which concentrated current travels is reduced. There is less carboniza-

Although widely used abroad, *arteriography* is employed only in exceptional cases in America. Gross<sup>4</sup> used a rapidly excreted iodide (diodrast) in 10 cases. Thirty cubic centimeters of a 70 per cent solution gave good results, but because of the recognized dangers, *i. e.*, hemiplegia and even death, he felt the procedure was only indicated "when accurate diagnosis is not possible by other methods and when a diagnosis is essential for guiding further treatment."

Another diagnostic procedure more favored abroad than in America is *cisternal encephalography*. Schorstein<sup>5</sup> re-

ported briefly on 60 such encephalograms done in 50 cases. After the needle was in place he removed as much fluid as he could, usually 50 to 60 cc. Between the removal of each 10 cc he allowed the brain to suck in enough air through the open needle to restore pressure equilibrium. In 3 cases he failed to obtain any fluid, and these proved to have posterior fossa tumors and tonsillar herniations. In the whole series, however, he obtained good filling with air in 90 per cent of the cases as contrasted with only 80 per cent successes when the lumbar route was used. There were no deaths and even the cases of posterior fossa tumor were made no worse.

Glaser and Blaine<sup>6</sup> studied the fate of *cranial fractures* by series of x-rays in known cases. They found that narrow, linear fractures in children may begin to fade as soon as 2 months after the injury and are usually unrecognizable in from 6 to 12 months. In adults, fading is not noticeable until about 7 months and the line does not disappear, as a rule, for 3 to 4 years. Occipital fractures were the most persistent.

The diagnostic significance of symptomatic *epilepsy* was studied statistically by Penfield and his associates.<sup>7</sup> Seizures were most common in lesions near the Rolandic fissure. Eighty per cent of tumors in the frontotemporal region and 71 per cent of those in the frontoparietal region produced convulsions. Seizures as a first symptom were commoner with the slowly-growing tumors than with the rapidly-growing ones. When a tumor was encapsulated, its removal stopped the convulsions twice as often as when an infiltrating tumor was present. In general, cerebellar tumors did not produce epileptic seizures. Webster and Weinberger<sup>8</sup> studied this latter point particularly, however, and concluded that focal or generalized convul-

sions do not exclude the diagnostic possibility of a cerebellar tumor.

### War Head Injuries

Reports on experiences with head injuries in the present war have begun to appear. The "*War of Movement*" or "*Blitzkrieg*" has introduced new problems in treatment. Adequate facilities for extensive neurosurgery are difficult to provide reasonably near to a rapidly shifting front line. Tönnis<sup>9</sup> saw fortunate outcomes in 52 cases who were evacuated by plane to Breslau or Berlin during the Polish campaign. Cairns<sup>10</sup> refers to a mobile unit with facilities and personnel for 2 simultaneous operations, and supplies for hundreds of neurosurgical operations.

Fortunately, the prophylactic use of the *sulfonamides* seems to be making it possible to delay operations much longer than was formerly thought safe (even up to 48 hours after injury). Amazingly low mortality rates appear in some series of cases. For example, Jefferson<sup>11</sup> lost only 5 out of 42 cases (12 per cent). In 1918, his mortality rate was 37.6 per cent. He believes that the bomb casing fragments are smaller, and as a result less infection is being driven into the brain from the skin than was often the case in the last war. The British type of helmet has not proved to be completely satisfactory because it leaves the mastoid and occipital regions exposed to injury.

### Lobectomy and Lobotomy

The changes to be expected after surgical intervention in 1 or both frontal lobes in man have not yet been clearly defined. Hebb and Penfield<sup>12</sup> report excellent adjustment by a patient in a simple social situation 15 months after considerable cortex had been removed from both frontal lobes. Formal tests revealed no serious defects in his intellect or per-

sonality Karnosh and Gardner<sup>13</sup> have seen similar adequacy in 4 patients from whom right cerebral hemispheres have been removed. Nichols and Hunt,<sup>14</sup> however, have studied a case of bilateral frontal lobectomy in great detail and have found a demonstrable deficit in the field of abstract behavior. The patient failed to supply spontaneous fresh modes of attack on a problem in which his failure was obvious, and even when separate plans of action were provided for him, he was limited in the number of plans he could keep separate simultaneously. These authors point out that "in thinking of psychosurgery, we must . . . realize we are substituting 1 disease for another, and although this may be a perfectly justifiable procedure in severe cases, it can never be used in those individuals whom we wish to return to a reasonably high economic and social life." Mixter and his associates<sup>15</sup> confirmed previous reports that subcortical section of white matter in the frontal lobes (lobotomy) can have a quieting effect on cases of agitated depression, but they recommend the procedure only in longstanding, severe cases who have been unresponsive to less radical therapy.

### Trigeminal Neuralgia

There is still a great deal of misunderstanding about the results of modern therapy in tic douloureux. Poppen<sup>16</sup> finds that many patients have been misinformed as to the dangers and complications of *root sections* by the temporal approach. Actually, the low mortality

of 1 per cent is almost negligible, and he does not believe that facial palsies appear in more than 5 per cent of the cases. On the other hand, some patients fear the pain of *alcohol injection*, and have heard exaggerated tales concerning the brevity of results with this procedure. Poppen feels it always should precede nerve section because rarely a patient is found who prefers the pain to numbness and paresthesia, and the alcohol injection permits such a patient to make his choice. Thorough training of the operator should precede any efforts to inject trigeminal branches.

Grant and his associates<sup>17</sup> relieved 12 patients by sectioning the pain fibers in the descending root of the trigeminal nerve in the medulla (Sjoquist, 1938). The old, temporal, approach is so safe that it should not be abandoned rashly, but the medullary section never produces numbness or paresthesias. It is an ideal approach in cases with malignant tumors of head and neck, since roots of glossopharyngeal nerve and upper cervical nerves can be sectioned at the same time.

*Atypical facial neuralgias* are sometimes very difficult to treat. They may or may not be accompanied by true tic douloureux. The atypical pain often seems to travel centrally over sympathetic fibers. When the distribution is *buccal*, Reichert<sup>18</sup> recommends the simple procedure of *sectioning the facial artery and vein with their sympathetic fibers at the lower border of the mandible*. Thirteen of 17 patients were relieved by this means.

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## CRANIAL TRAUMA

By ROBERT A. GROFF, M.D.

**Statistics**—The value of statistical reviews of a large series of cases lies in the fact that treatment may be adjusted

to facts rather than impressions. This is particularly so in patients suffering from head injuries. Several excellent reviews

have been presented during the past year. Briesen<sup>19</sup> has reviewed a series of 5912 cases of head injury and divided these cases into 2 groups, (1) a major group of 1969 (33.3 per cent) which included those patients with definite cerebral damage, with or without skull fracture, all patients with skull fracture, and all patients which developed complication; (2) a minor group of 3943 (66.6 per cent) which included those patients with no evidence of brain injury and no skull fracture.

The causes for the head injuries in these cases were:

Automobile .. .	61.0%
Falls .. .	15.9%
Assaults .....	11.6%
Miscellaneous .. .	4.1%
Motorcycle .....	1.9%
No history . . . . .	5.4%

The gross mortality for these cases was 7.5 per cent. The mortality for the patients in the major injury group was 22.6 per cent. Of the deaths, 51 per cent occurred during the first day; 79 per cent by the fifth day, and 90 per cent by the eleventh day. The author's comment upon these figures is that movement of the patient reduces the chances for recovery. He feels that a number of patients would not have developed serious intracranial complications if they had not been moved. The high percentage of first-day deaths is undoubtedly due to the original injury, but reactions to the injury are probably responsible for an equally high number of deaths. These reactions are increased by movement of the patient, administration of fluids, and surgical procedures.

The significant points obtained from this review, from both the prognostic and therapeutic standpoint, are as follows:

An *unconscious period* was present in 50 per cent of all cases and 53 per cent

of cases in the major group. The combined unconscious and semiconscious data indicated that an unconscious patient, who awakens to a rational state, has a much better chance for recovery than one who awakens to a semiconscious state. The author issues the warning against the belief that the length of consciousness indicates the severity of brain damage, and states that short periods of unconsciousness, or no history of unconsciousness, should not relax the vigilance of the surgeon. Meredith,<sup>20</sup> on the other hand, feels that the unconscious period is the most important single factor in prognosis. The longer the period of unconsciousness, the more serious the brain damage.

*Objective evidence* in the severely injured patients was absent in 7.4 per cent. By reason of this figure, the possibility of a head injury should be considered in every patient with loss of consciousness, particularly when the diagnosis of a vascular accident has been made.

*Subjective evidence* was found to be present in only 28 per cent of patients and, therefore, must be very carefully evaluated before it is given consideration in estimating the degree of injury.

The author's statistics further emphasize the fact that *skull fracture* is not a cause of death, 546 patients, with skull fracture, having recovered without special treatment. As the author states, however, if a skull fracture is present, the probability is that the brain injury is more severe.

*Treatment*—In these patients the treatment consisted in *absolute and prolonged bed rest, control of intracranial pressure, maintenance of tissue nourishment*, both general and local. These were accomplished by *sedatives, noninterference, dehydration, lumbar puncture, intravenous*

***hypertonic solution, tube feedings, surgery.***

Meredith emphasizes the fact that direct palpation of all lacerations of the scalp, with a gloved finger, should be made to establish compound depressed fractures. He further emphasizes that nasal-tube feedings should be more widely used for any unconscious or semi-conscious patient. In patients with cerebrospinal fluid leaks, from the cranial orifices, *sulfanilamide* should be given.

In Brieson's review, *surgery* was employed in 3.3 per cent of the 5900 patients. The reason for operation was removal of depressed fragments 52 per cent; control of increased intracranial pressure by subtemporal decompression 25 per cent; extradural hematoma 5 per cent; subdural hematoma 10 per cent. In 15 patients, or 13 per cent of the operations, massive subdural fluid collections were found. These fluid collections were not recognized clinically. According to both Brieson and Meredith, *trephining* has replaced, to a great extent, the procedure of subtemporal decompression, since it is effective in relieving fluid collections.

The *complications* which caused death were edema, diffuse hemorrhage, contusion and lacerations of the brain, massive hemorrhage, fluid collections, as well as infection. The most important factor brought out by the study of the complications is that 16 per cent of patients in the upper age group were found to have massive subdural hemorrhage. Age, therefore, should not be considered a factor in the cause for poor reaction following head injury. Brieson states that some of these patients might have been saved if the diagnosis had been made.

**Posttraumatic Sequelae**—The incidence of posttraumatic sequelae, with

special consideration of "*traumatogenic general cerebral syndrome*" is presented by Saethre.<sup>21</sup> The material used was a series of 589 cases; 258 were early and 316 were late injuries. Alcoholism was found to be an important factor in that 30 per cent of the new patients were under the influence of alcohol when admitted to the hospitals, and one-third of the patients with traumatic psychosis were chronic alcoholic addicts. Loss of consciousness persisted in three-quarters of the patients for less than 2 hours. Of those in which loss of consciousness persisted for more than 24 hours, only 6 presented the pure syndrome of commotio cerebri. On the other hand, the syndrome of commotio cerebri existed in 67.5 per cent of head injuries.

Neurological disturbances were observed in 54.7 per cent of the new cases and 35 per cent of the late cases. In more than one-half of the late cases otologic symptoms predominated. Olfactory paresthesias and anosmia were likewise relatively frequent. Traumatic epilepsy was observed in 5 per cent.

The author regards it as inadvisable to apply the term "*traumatic neurosis*" to the subjective symptoms of patients with head injuries; he considers that this term should be restricted to cases in which intracranial lesions are absent. He suggests that the subjective symptoms be classified into (1) the traumatogenic cerebral general syndrome (headaches, vertigo, and difficulties in thinking), and (2) psychogenic symptoms (*a*) primary, those due to shock, and (*b*) secondary, the psychoreactive and compensatory symptoms. The traumatogenic cerebral general syndrome predominated in 49.4 per cent of the cases, the psychogenic symptoms in 24.8 per cent, and the organic neurologic symptoms in 25.77 per cent.

## BRAIN TUMORS

By ROBERT A. GROFF, M.D.

### Colloid Cysts of Third Ventricle (Paraphyseal Cysts)

With the report of 4 cases, Shaver<sup>22</sup> again discusses the question of origin of colloid cysts of the third ventricle. In 2 of his patients the cysts were removed successfully and in the remaining 2 they were found at autopsy.

The clinical features in these 4 cases were remarkably similar. All the patients were women and their ages ranged from 19 to 28 years. The history in 3 patients was recurrent attacks of headache with or without attacks of vomiting over a period of 2 months to 2 years. The third patient had recurrent attacks of blurred vision. All patients presented a normal neurological examination except for bilateral papilledema. The diagnosis was made in the 2 operated patients by ventriculogram, which showed absence of filling of the third ventricle.

All the cysts were observed hanging from the anterior portion of the roof of the third ventricle and intimately associated with the choroid plexus in this region. They measured approximately 1 to 2 cm. in diameter and presented a rather smooth, thin, fibrous, wall over which ran numbers of blood-vessels. Villi of the choroid plexus were adherent in 2 cases. In each instance, the only content was a greenish or grayish, translucent, gelatinous "colloid" substance, while microscopically the wall was lined on its inner surface with a characteristic columnar epithelium which was ciliated in some cases.

Shaver agrees with McLean in that these cysts have been found only in the third ventricle, which suggests their origin from some structure to be found only in that region. If they were only

cysts of the choroid plexus one would expect to find them as frequently in other sites where the choroid plexus is present. He feels that the most reasonable explanation of the origin of these cysts is that they arise from the paraphysis, which is an embryonic structure derived from the fetal ependyma of the anterior portion of the roof of the third ventricle. The histological structure seems to support this view, as tubules are frequently observed in their walls and suggest origin from a glandular structure.

### Tuberculomas of Brain

Tuberculomas constitute a very small percentage of verified tumors of the brain. This fact and the general belief that surgical removal of these lesions meets with little success has led Buchstein and Adson<sup>23</sup> to review the literature and re-examine 12 of their own cases. In 6 of these, operation was performed.

It is pointed out that the tubercle bacilli may reach the brain and its coverings in 3 fashions. The most obvious and direct route is by the growth of a contiguous lesion. It has been suggested that tubercle bacilli may pass from tuberculous lesions in the nasal and pharyngeal cavities to the cranial meninges by way of the perivascular lymphatic channels accompanying some of the cranial nerves. No adequate proof, however, of such a migration has been presented. It is generally agreed that the great majority of tuberculous lesions of the brain arise by metastasis *via* the blood stream from foci which may be confined to 1 organ (usually the lungs) or may be generalized.

The *pathological characteristics* of tuberculoma are similar to those of tuber-

culous lesions in other organs. In the brain, tuberculoma are the product of mesodermal tissues, *i. e.*, the meninges, the vascular tree, and the microglia. These authors concern themselves with focal tuberculous lesions, *i. e.*, masses of tuberculous granulation tissue.

From a *clinical standpoint*, tuberculomas may be divided into those which are asymptomatic and those associated with clinical evidence of intracranial disease. The asymptomatic tuberculoma probably escapes detection because the brain is not examined or because the lesion is small, escaping detection or recognition. The tuberculomas associated with symptoms of intracranial disease may be divided into 2 groups. In the large group, the symptoms are exclusively or predominantly those of tuberculous meningitis. In these the tuberculoma is more often small and multiple. In the smaller group, the symptoms are attributable to the tuberculoma itself. As is true, of other types of brain tumor, these may be localizing in character or simply indicative of increased intracranial pressure.

These authors conclude that tuberculomas which produce symptoms of cerebral tumor tend to occur at all ages and in persons who have but a single extracranial tuberculous focus, usually in the lungs, or the associated lymph-nodes. Tuberculomas that are associated with the clinical picture of meningitis, on the other hand, occur predominantly in the early years of life and in association with generalized tuberculosis. They state that these observations are, of course, to be regarded as trends and not as fixed rules.

The meningeal tuberculomas are epidural tuberculoma; pachymeningitis, externa tuberculosa, tuberculoma of the dura, and arachnoid tuberculoma (local-

ized tuberculous leptomeningitis). These are relatively uncommon. Epidural tuberculoma are favorable surgical lesions, since they rarely penetrate the dura to cause meningitis. Arachnoid tuberculoma are considered as relatively favorable subjects for surgical treatment by either extirpation or simple decompression. When removed surgically, they must be excised with a margin of surrounding brain tissue.

Fibrocaceous (intraencephalic) tuberculomas are the most commonly encountered granulomatous lesions of the brain. These lesions occur as frequently during the first decade of life as during all the years thereafter; are twice as frequent in men as in women; are single in two-thirds of patients, and they occur as frequently in the posterior cranial fossa as in the entire supratentorial region. In only 20 per cent of cases does the tuberculoma lie near or in contact with the surface of the cerebral convexities. The granuloma may become calcified.

The *surgical results* show that tuberculomas, within the cerebral hemispheres, can be removed successfully. In the 21 cases of complete surgical excision, reviewed by the authors, 1 patient died after the operation, 6 patients died at intervals varying from 11 to 24 months, 2 of tuberculous meningitis, 3 of pulmonary tuberculosis, and 1 of a second tuberculoma of the brain. Tuberculoma in the cerebellum have not been removed without the development of tuberculous meningitis. The reason given by the authors, for the unsuccessful treatment of cerebellar tuberculomas is that the inflammatory process extends along the interfolial septums of pial tissue far beyond the ostensible limits of the tumor. What appears, therefore, to be complete removal of such a tuberculoma will usually actually be incomplete.

### Hyperostosing Meningiomas of Sphenoid Wing

A rather interesting type of meningioma which primarily involves the sphenoid wing and produces thickening of this bone and the roof of the orbit is discussed by Poppen and Horrax.<sup>24</sup> The tumor of the bone occasionally gives rise to a globular intracranial mass, but more

ward. Roentgenograms verify the diagnosis, since they demonstrate an eburnation of the pterional region.

The *histological features* of this tumor are a notoriously slow growth and a tendency to remain primarily in the bone.

*Treatment* consists in **removal of all the diseased bone**, as well as that portion of the *tumor which involves the*

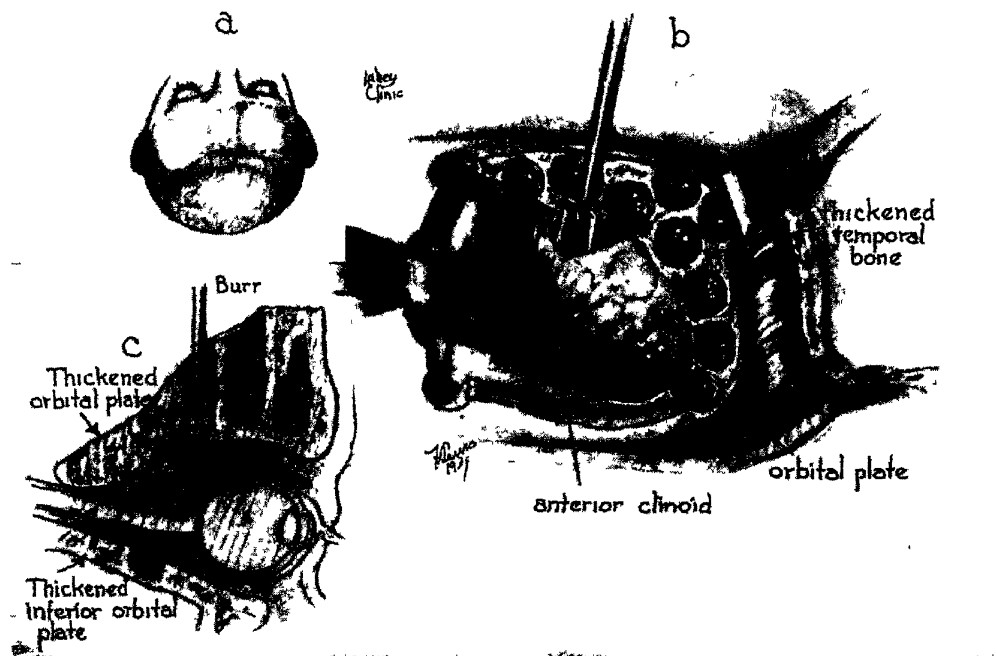


Fig. 1—*a*, Modified coronal incision with osteoplastic flap outlined *b*, Greatly thickened pterional plate, orbital bone, and anterior clinoid; demonstrating multiple burr openings. *c*, Greatly thickened orbital plate and inferior orbital plate with outlines of burr openings (Poppen and Horrax: Surg. Gynec. and Obst.)

commonly is a flat tumor lying on the dura and is called *meningioma en plaque*. This type of lesion, because of the involvement of the bones of the orbit, produces an exophthalmos.

The *clinical features* of this lesion are a slowly developing exophthalmos with diminished vision of the eye, swelling in the temporal region, usually caused by tumor infiltration, frontal headache, and pain in the eye, forehead and temple. The exophthalmos may be slight or marked, is nonpulsating, irreducible, and the eye is displaced forward and down-

**dura and extends into the cranial cavity.**

The technical features which have been worked out by these authors are worthy of mention. The dura, after a craniotomy has been performed, is separated from the orbital plate posteriorly, well over the greatly thickened sphenoid ridge, optic canal, and anterior clinoid, and also along the temporal bone laterally. The temporal muscle, if not invaded with the tumor, is separated from the bone on the lateral surface of the orbit and pterional region. The thick-



ened bone is now removed with giant rongeurs as deeply toward the triangle of the ala magna as possible. The greatly thickened and broad surface is honey-combed with the electric drill, and the interlacing remnants of bone removed with rongeurs. The orbital plate is then removed with the use of the electric drill and rongeurs, care being taken so that the orbital capsule is not injured, since, if it is unintentionally opened, considerable embarrassment is experienced because of the protrusion of fat tissue.

Since the inferior wall of the orbit as well as the lateral walls are also greatly thickened, in the advanced cases, the burr again can be used to great advantage, the burr openings being made close to each other, so that the partitions left may be removed readily with the rongeur. In this manner, all the bone may be removed from the orbital roof, side wall, and greater sphenoid wing to the superior orbital fissure. The portion of greatly thickened bone which covers the optic foramen and the greatly thickened anterior clinoid remain. In a few patients, the hyperostosis over the anterior clinoid may resemble a turret and be 2 to 3 cm in thickness. It readily can be understood that if any of the vision is

to be restored, this bone must be removed, and naturally, this step is the most hazardous. To remove the bone safely, a special drill about 2 mm in thickness was made with an adjustable sleeve so that the depth could be gauged readily. With this drill attached to the electric motor, many small openings are made 2 to 3 mm apart, within a few millimeters of the entire thickness of the bone. The greatly weakened structure is then removed by the judicious use of the mallet and chisel, small fragments breaking off without much jar or danger of breaking into a sinus. In this manner, the entire anterior clinoid is removed, and the superior orbital fissure and optic canal are left well decompressed. The orbital capsule is then widely opened and the intraorbital tissues are allowed to protrude. They are examined for the presence of tumor. The incision should start over the annular ligament of Zinn and be carried upward, since in this way the protruding tissues do not interfere with completing the opening of the capsule. The dura is opened and if a *tumor* is present, it is *removed*, or if only a *thin granular layer of tumor* is found, it is thoroughly eschared with *electrocoagulation*.

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## SPINAL CORD TUMORS

By ROBERT A. GROFF, M.D.

### Tumors of Foramen Magnum

Tumors which arise in the region of the foramen are uncommon, but are in the great majority of instances benign lesions. The types most frequently encountered are meningiomas, and neurofibromas, although malignant growths may occur.

The syndrome of tumors in this location has been discussed by Weinberg,<sup>25</sup>

who reports 2 cases and reviews the literature. According to this author, the most significant clinical feature of these patients, which should bring into consideration this diagnostic entity, is pain in the cervical region, at times in the occipital region, tending to extend down both arms to the elbows and aggravated by muscular efforts involved in coughing, sneezing, and other exertions. The

march of symptoms otherwise seems to depend on the extent of the tumor and the direction of growth. When these tumors project into the posterior fossa, symptoms of intracranial pressure occur, such as nystagmus, papilledema, vertigo, ataxia, past-pointing, and asteriognosis. Signs which may be present but are not especially characteristic of spinal cord tumors are high or moderately high protein levels in the spinal fluid, partial or complete spinal block, paresis, of infra-buccal facial nerves, atrophy of the muscles of the upper extremities, and speech difficulties.

The author points out that the early recognition of these tumors affords a greater chance for removal, with lower morbidity statistics.

### Cervical Cord Tumors

A series of 91 tumors of the cervical portion of the spinal cord has been reviewed by Craig and Sheldon.<sup>26</sup> This paper is important for 2 reasons, *i. e.*, (1) tumors of the cervical portion of the spinal cord are not common, and (2) the signs and symptoms of these tumors are sufficiently characteristic to lead to a diagnosis.

The *types* of tumor represented in this series of 91 cases are as follows: Extradural tumors, 22 (12 were neurofibromas, 6 were protruded intervertebral discs, 2 were chordomas, 1 was a tuberculoma, and 1 was a granuloma); 44 intradural tumors (1 angiomaticous varix, 2 hemangioendotheliomas, 4 hemangiomas, 16 neurofibromas, and 21 meningiomas); 19 intramedullary growths, 6 intra- and extradural growths. All were neurofibromas of the so-called dumbbell type.

The *signs and symptoms* of cervical cord tumors which are of special importance, according to these authors, are pain in the neck, as an early symptom,

muscular weakness beginning in the arms but may involve the legs as a progressive symptom, and dissociation of anesthesia as a constant accompaniment of all types of lesions of the cervical portion of the cord, but not in itself diagnostic of any 1 type of lesion. Sphincter disturbances of variable degrees were present in many of their cases but were not of diagnostic or localizing value.

The authors employ a hemilaminectomy on the side of the tumor for exposure and removal. They feel that this operation gives adequate exposure without sacrificing the stability of the vertebral column.

### Herniation of the Nucleus Pulposus and Hypertrophy of the Ligamentum Flavum

The intervertebral disc and ligamentum flavum have been receiving considerable attention in the literature during the past several years. The cause for this sudden interest is the establishment of the relationship of low-back pain and sciatica to the structures when they become diseased. This relationship has been proven by the relief of pain following the removal of a herniation of the nucleus pulposus and or hypertrophy of the ligamentum flavum. The wealth of material relating to this subject in the literature affords a rather thorough review of present knowledge about these structures and the part they play in the production of sciatica and low-back pain.

**Anatomy and Physiology**—According to Naffziger, Inman and Saunders,<sup>27</sup> the space between each 2 vertebral bodies is occupied by the intervertebral fibrocartilaginous disc. The intervertebral discs vary in vertical thickness in different parts of the vertebral column. They are thinnest from the third to the seventh thoracic vertebra and thickest in the lumbar region. In both lumbar and

cervical regions each disc is thicker anteriorly than posteriorly, in this wise assisting in the production of the anterior convexities which characterize the vertebral column in these regions. In the thoracic region, the reverse occurs in the correspondence with its anterior concavity.

*Histologically* each disc consists of 3 parts. The first portion is composed for

is a soft, pulpy, elastic center which is called *nucleus pulposus*. It serves as an elastic ball-bearing, changing in shape and position as the force and stress demand of it. In the lumbar region, the nucleus pulposus is placed a little dorsal to the center of the disc, and in flexion it tends to move in a still more dorsal direction. The third portion of the disc is the cartilaginous plates which are the



Fig. 2—Dissection of right posterolateral wall of vertebral canal in lumbar region. Attachments and extent of ligamenta flava clearly shown. (Naffziger, Inman and Saunders Surg. Gynec. and Obst.)

the most part of oblique and spirally arranged fibers passing from 1 vertebra to the other. In section, this portion is arranged in a series of concentric lamellae and has received the name of *annulus fibrosa lamellae* or fibrosus. The annulus is attached into the substance of the bone by the fibers of Sharpey. It is further supported by a very wide well-defined anterior longitudinal ligament, and a less well-defined posterior longitudinal ligament, giving support in the center only. The second part of the disc

bearing surfaces of the contiguous centers, thus giving a drum-like form, according to Schmorl.

The *ligamenta flava*, on the other hand, consists predominantly of yellow elastic tissue. This ligament extends between the laminae to which it is attached, and this attachment is marked by a groove in the bone. The lateral extensions of the ligament blend with the capsule of the interarticular joint, separating this structure from the neural canal, and are attached to the pedicle of the

vertebra above and below. The free edge of the ligament forms approximately one-half of the intervertebral foramen through which the spinal nerves pass (Fig. 2).

From this anatomical description, the mechanism for pain production, when a nucleus pulposus herniates posteriorly or a ligamentum flavum becomes hypertrophied, readily can be seen. The resultant pathology causes pressure upon the spinal nerve-roots. Since this type of pathology occurs most frequently in the lumbar region, it is associated with low-back pain and sciatica.

**Etiology**—Most authors assert that the cause for either disease entity is trauma, although the herniation of the nucleus pulposus may occur spontaneously. Love and Walsh,<sup>28</sup> in an analysis of 500 cases, report a positive history of trauma in 58 per cent. Naffziger, Inman, and Saunders<sup>27</sup> ascribe the hypertrophy of the ligamentum flavum to rupture of fibers with repeated trauma, scar formation, and subsequent hypertrophy of the scar.

**Neurological Signs and Symptoms**—According to Spurling and Grantham,<sup>29</sup> the location of the protruded nucleus pulposus or hypertrophied ligamentum flavum can be recognized clinically. The signs and symptoms which they give are as follows:

#### Lumbar III:

1. Disability of the lower part of the back (with local tenderness at the third lumbar spine and reduction of lumbar lordosis).
2. Positive Lasegue sign.
3. Positive Naffziger sign (producing paresthesias in the fourth and fifth lumbar dermatones).
4. Reduction or absence of knee-jerk, with an unchanged ankle-jerk.
5. Hyperesthesia and paresthesia in the fourth and fifth lumbar dermatones.

#### Lumbar IV:

1. Disability of the lower part of the back, with stiffness of the lumbar portion of the spine.
2. Local tenderness at the level of the fourth lamina with reduction of lumbar lordosis.
3. Positive Lasegue sign.
4. Positive Naffziger sign—paresthesias involving the fifth lumbar and first sacral, possibly second sacral dermatone.
5. Uninvolved ankle- and knee-jerks.
6. Hyperesthesias and paresthesias in the fifth and first sacral dermatones.

#### Lumbar V:

1. Disability of lower part of back, with absence of lumbar lordosis, and localized tenderness to pressure over fifth lumbar vertebra.
2. Positive Lasegue sign.
3. Positive Naffziger sign—producing paresthesias radiating into first and second sacral dermatones.
4. Diminished or absent ankle-jerk
5. Hyperesthesia involving the first and second sacral dermatones.

These authors attest these signs and symptoms by the fact that they have operative verification of a number of patients without lipiodol assistance.

Stookey<sup>30</sup> states that herniation of the nucleus pulposus in the cervical region produced 2 types of clinical syndrome.

The first is in those patients where the protrusion is small and in the mid-line, bilateral pressure is exerted on the ventral horns of both sides and on both ventral roots, giving rise to bilateral signs referable to the ventral gray columns, without evidence of compression. This picture causes focal atrophy and cross-dissociated sensory changes. Unilateral root pressure is characterized by unilateral focal atrophy and focal pain without signs of involvement of the long fiber tracts.

The second syndrome is produced by large herniations where the symptoms

and signs are indistinguishable from a ventral tumor of the spinal cord.

Symptoms may be constant or intermittent. In Walsh and Love's<sup>28</sup> series, 84 per cent of the 500 cases had periodicity of pain. A similar reference to intermittent pain is made by Macey<sup>31</sup>. This author also offers the explanation for the attacks of pain by the fact that the nucleus pulposus may at 1 time be herniated and at another time in normal position.

**Location**—The greater number of herniations of the nucleus pulposus are in the lumbar region and chiefly of the third, fourth, and fifth lumbar intervertebral disc. They may, however, occur in the thoracic and cervical region. So far as can be determined, hypertrophy of the ligamentum flavum has occurred only in the lumbar region.<sup>27</sup>

**X-ray Diagnosis**—From the reported articles, plain films of the spine do not give any information. A contrast medium is necessary to demonstrate these lesions on the x-ray film. Some authors prefer air (Chamberlain), while others prefer lipiodol (Macey, Naffziger, Stookey). Spurling and Grantham claim that in most patients contrast media is not necessary.

**Treatment**—The operation of *laminectomy* has proven to be the treatment of choice. All authors report favorable results. Macey<sup>31</sup> states that the articular facets should be preserved during the operation. Walsh and Love,<sup>28</sup> Hamby,<sup>32</sup> and Stookey<sup>30</sup> prefer *hemilaminectomy* and the former writers report 1 case in which the disc was removed without taking away any bone. Mixer and Barr<sup>33</sup> do a *partial laminectomy*, removing part of the lamina above and part of the lamina below the involved intervertebral disc. It is the Reviewer's opinion that a laminectomy is preferable to hemilaminectomy, since it is just as important to remove the ligamentum flavum as the herniation of the nucleus pulposus and, further, both sides should be inspected.

Walsh and Love report 5 recurrences, all at the site of the previous operation. Pennybacker<sup>34</sup> states that in some patients the herniation is due to a protrusion of the annulus fibrosa, and the results of operation are not as satisfactory as in herniation of the nucleus pulposus. With present knowledge, he feels that the 2 conditions cannot be differentiated.

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## PERIPHERAL NERVES

By ROBERT A. GROFF, M.D.

### Nerve Regeneration

Some interesting studies have been made by Young<sup>35</sup> and his associates upon the regeneration of peripheral nerves. These studies give valuable information in formulating the best surgical treatment.

Young found in experiments on rabbits that the central stump grew at the rate of nothing, in cases in which a

bulb was formed, to 0.4 mm. a day. The average rate of growth was 0.2 mm. a day. The peripheral stump, on the other hand, showed a rate of growth from 0.45 mm. to 1 mm. a day. The peripheral stump, therefore, grows more rapidly than the central stump, a fact which heretofore has been overlooked.

When a gap of not more than 2 cm. exists between the 2 stumps, the rate

of growth may be as much as 0.77 mm. to 1.3 mm. a day. In this study, the authors felt that the majority of the growth occurred from the peripheral stump.

The authors state that the Schwann cells from the peripheral stump can and do adequately bridge gaps between the cut end of the nerves. They have the impression that there is some attracting and accelerating force exerted by the central stump on the cells of Schwann. It is important to realize the part played by these cells in regeneration when instituting treatment.

Experiments were made with different types of grafts such as autografts, predegenerated autografts, homografts, stored homografts, and alcohol-fixed homografts, to determine their effect on regeneration. The results of this work led the authors to conclude that the ends of the nerve should be guarded against pinching or other maltreatment. Thin autografts insured the best results and a cable graft of several thin strands was probably better than a single thick graft. The importance of this study lies in the fact that successful regeneration depends on the active contribution of the living Schwann cells of the peripheral stump, and the grafts should be treated as a living thing.

### **Fibrin Suture of Peripheral Nerves**

Young and Medawar<sup>36</sup> have presented a method by which cut nerve-ends can be held together by a concentrated coagulated blood plasma. The advantages of this method are the reduction of difficulties of nerve suture, minimizes the disorganization of the fibers which is likely to be caused by sutures, and the growing fibers are more likely to grow directly between the ends of the cut nerves without deviation, according to these authors.

The method consists in holding the nerve-ends together and pouring around them plasma which has been mixed with strong tissue-extract. The plasma firmly jells in 1 to 2 minutes and holds the stumps together. Subsequently, the plasma dissolves away but not until sufficient time has elapsed to permit a free passage of nerve-fibers and a firm union.

Ordinary plasma does not form a jelly which is strong enough to maintain fixation under tension. Cockerel plasma has proved the best. Blood is withdrawn from the carotid artery through oiled cannulas into large centrifuge tubes. These are packed in ice for 10 minutes and then spun. The supernatant plasma is stored in waxed test-tubes on ice and keeps for at least 6 weeks. The animal should be starved for 36 hours before. No heparin need be used. The concentration is effected by the precipitation of fibrinogen (with prothrombin) from part of the plasma and by its resolution in a smaller volume. The concentration thus concerns only the protein constituents. Mellanby's method is used, 1 volume of plasma being mixed with 9 volumes of redistilled water and then slowly with from 0.1 to 0.15 volume of a solution of acetic acid in redistilled water containing 1 per cent by volume. The fibrinogen forms a flocculate, which is centrifuged out after standing for 5 minutes. The supernatant fluid is discarded and replaced with water, which is also taken off with a fine pipette. The fibrinogen may now be either used directly or stored under distilled water at 4° C. It keeps for at least 10 days. Before use, the fibrinogen is dissolved in plasma—not in saline solution, because in the presence of serum, the fibrin clot is stronger and much more stable. The

quick and even coagulation of the plasma is ensured by mixing it thoroughly just before application with not more than a one-tenth of its volume of a concentrated tissue-extract. Chicken-embryo extract in saline solution (2 cc. for a 10-day embryo) is satisfactory.

The resulting plasma mould about the nerve stumps acts as a protectorate and little or no plasma comes between the nerve-ends. Thus, an ideal situation is presented in that no barrier is set up to inhibit the growth of both the peripheral and central ends of the nerve. This method is especially valuable in suturing of small nerves.

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## ORTHOPEDICS

*Edited by* JOHN ROYAL MOORE, B.S., M.D.

### STATIC DISABILITIES

*By* JOHN G. KUHN, M.D.

Static disabilities are occupying an increasingly important place in the field of public health, particularly in the present attempt to secure the best possible physi-

cal fitness in the people of the nation. Educators and public health officials have sought methods of preventing these disabilities during childhood. While some

progress has been made by more careful examinations by school physicians, followed by treatment through special exercises to secure better coordination and balance in the supporting structures of the spine, the majority of children are growing up with bad posture associated with static disabilities in various parts of the body.

More recently it has been shown that a more effective attack can be made to *prevent* these *disabilities* by starting in infancy. The proper resistance of the muscular structures of the body to the force of gravity is developed through conditioned reflexes. These can be formed in infancy before bad habits of carriage have been learned. For this, it is necessary that the baby lie flat on a firm bed so that the spine is straight in recumbency. Sitting should only be permitted when the child is strong enough to do it without assistance. When sitting, the back should be straight without any forward bowing of the spine. A firm pillow can be used for support against the back. Standing should be permitted only when the child is strong enough to do so. Then he should be encouraged to hold the head erect, the chest up, the abdomen in, and to point the feet forward without placing the foot in valgus. To give instruction in these things takes very little extra time on the part of the mother or nurse. By the time the child is walking well, proper habits of carriage, with correction of any early static deformities, will have been obtained.

If static disabilities are not corrected early in the growing years, permanent osseous deformities may develop. One of the commonest places for this to occur is in the spinal column. The vertebrae are dependent to a large extent for their normal growth upon the stresses and muscular pulls that come upon them. If the spine is used habit-

ually with an increase in the antero-posterior curves or with a lateral curve, the vertebrae will grow to fit this position and a permanent slight wedging of the vertebrae will result. In like manner, the scapulae will become more convex on their flat surface to fit the changed contour of the thoracic cage. Because the center of gravity is displaced forward, an internal rotation occurs in the necks of the femora and at the knee. Here, too, lasting deformity can occur from faulty statics during growth.

*Symptoms* the result of static deformities during childhood usually present themselves as fatigue, muscular aches and more or less obvious deformities. It is only in adult life that a great number of vague symptoms are found which are now known to be caused by static disturbances. A large number of the backaches seen particularly in industry, have their origin in a faulty mechanical use of the back. In low-back injuries the twist or unguarded movement, which results so often in pain and muscular spasm, is only the final episode where the lumbar spine has been used at the extreme of extension for a long time. In many of the other pains referred to the surface of the thorax and abdomen it has been shown that they have no relation to the viscera within, but are the result of irritation of the intercostal nerves. The cause of this irritation of the nerves was found to be faulty posture, the symptoms disappearing when the posture was corrected. On further study of these pains it has been found that the source of irritation was frequently located in the costovertebral joints<sup>1</sup> which are quite close to the intercostal nerve roots at their point of emergence from the neural foramina. Strain of these joints from a downward displacement of the ribs when the body



is used badly leads to irritation of the nerves.

Cardiologists have come to recognize the increased burden that is placed upon the pulmonary circulation when serious static deformities affect the thorax. They have given it the name *cardiopulmonary syndrome*. The chain of events that leads to right-sided heart-failure is somewhat as follows: The flattening of the chest leads to decreased vital capacity and to nonexpansion or decreased expansion of a number of the alveoli. This in itself, as in funnel chest and scoliosis, leads to interference with the normal flow of blood in the parenchyma with passive congestion. Pressure in the pulmonary arteries increases with hypertrophy and eventual failure of the right side of the heart.

In the treatment of *deformities of the thorax*, which can lead to circulatory interference, whether these deformities are congenital or acquired, the principles originally described for the correction of static disabilities are helpful. By the *correction of faulty body mechanics* and the continuance of *breathing exercises* for several years, most symmetrical deformities of the thorax can be corrected and the asymmetrical ones can be improved. The mechanism which corrects these deformities is the pull of the diaphragm and the accessory respiratory muscles upon the thoracic cage. In normal deep breathing the ribs are rotated outward and upward and the sternum is lifted upward and forward. If the diaphragm is low, as is often found in faulty body mechanics, the lower part of the sternum is pulled directly inward in breathing.

The problem of static disabilities is closely related to the proper development and function of the *feet*. This has been shown in a number of recent contributions.<sup>2,3</sup> In the usual valgus de-

formity, the commonest evidence of weakness in the foot, the valgus deformity usually is related to faulty posture.<sup>4</sup> With the increase of lumbar lordosis and with the increased forward inclination of the pelvis, the center of gravity is shifted anterior to the acetabuli. To compensate for this shifting of the weight thrust, the femoral columns rotate internally so as to come more squarely under the weight. Since no rotation is possible at the knee or ankle joints, the internal rotation of the shaft of the leg is accompanied by an adjustment in the posterior tarsal joints, producing a valgus of the os calcis and a prominence of the inner side of the foot. The forefoot, by this movement, is pushed into eversion and abduction. This process can be seen most readily in slender children. But the combination of bad posture and weak feet is also the most common type in adults.

There are other, somewhat less common, types of weakness in the foot. One type is the result of structural changes in the bones or muscles. A valgus of the posterior part of the foot may result from a contracture of the tendo Achillis. When this heel cord is short, there is difficulty in getting the heel to the ground in walking and to make up for this shortness the os calcis turns in a valgus direction. In women, this shortness is produced and then compensated for by high heels. In such cases, foot strain results when low heels are worn. Another fairly common structural change is a relative shortness of the first metatarsal bone. This causes the weight which should normally be borne on the first metatarsal head to be shifted to the second metatarsal or the more lateral metatarsal bones, resulting first in strain and discomfort in the forepart of the foot and with strain coming later in the whole foot.

It is appropriate at this point to mention the changing concept in the commonest developmental change in the tarsal bones, *i. e.*, *Köhler's disease of the tarsal scaphoid*. In this condition the scaphoid bone becomes thinner than normal, almost coin-shaped, and in roentgenograms it casts a much denser shadow. The cause is unknown, but the weight of evidence suggests that the condition is produced by a circulatory disturbance. It is sometimes found in children who complain of pain and stiffness in the mid-foot, but it is seen just as frequently in children who have no symptoms. Studies of these children for a period of several years show that this is a self-limited condition, with complete anatomical restoration in practically every instance. If symptoms are troublesome in this condition they can be relieved readily by *strapping* or by a *support* worn *under the foot*, holding up the arch under the scaphoid bone.

Related to this, but a more serious condition, is "*march foot*" and *infracture of the second metatarsal bone*. Both of these conditions are related to faulty statics. March foot, has been described as an incomplete fracture and as a twisting of the metatarsal bones; fatigue and nutritional disturbances have also been looked upon as causes. Infracture of the second metatarsal bone was thought to be an epiphyseal disturbance but more recent evidence points to an incomplete fracture from various causes. In both of these disturbances treatment is the same as for a fracture, *i. e.*, *temporary avoidance of weight bearing* followed by a *plate* or *pad* which gives support just *back of the metatarsal heads*.

Another type of disability in the foot is the *arthritic foot*. Practically every disability of the feet that has not been cared for before middle life will show arthritis. The most serious of these will

be found associated with a generalized rheumatoid arthritis. Often, *avoidance of weight bearing* for a month or longer is necessary to bring about a subsidence of symptoms. Here, everything that produces strain must be eliminated. This includes *correction of faulty posture, strengthening of the supporting muscles of the feet* and proper alignment of the foot with whatever support is required, *i. e.*, *plates, braces, strapping*. At the same time, the general arthritis should be treated. Most of these individuals with arthritis involving the feet can be so improved that they can again follow their occupation. Where much *deformity* of the foot has occurred from a severe arthritis of long duration, *manipulation* or *operation* may be required to secure a good weight-bearing position.

In older persons *circulatory inefficiency* in the extremities often first makes itself evident by pain in the feet. The circulatory disturbance leads to muscular weakness which secondarily produces weakness and strain in the feet. The cramp-like pains in the muscles, the intermittent claudication, is also at times mistaken for foot strain. This circulatory disturbance is commonly the result of *arteriosclerosis, Buerger's disease* or *Raynaud's disease*. In the treatment of these diseases, *proper balance* and *support of the feet* will help much in maintaining a satisfactory local circulation and often prevent the development of symptoms. Here, too, *correction of the faulty posture* is a helpful measure in improving the circulation of the whole body. In all patients who complain of disability in the feet, the circulation of the feet should be determined.

A résumé of the newer knowledge of the foot would be incomplete without a discussion of *proper shoes*. With an in-

creasing number of urban dwellers walking all their lives on hard surfaces has come an increase of disabilities of the foot. It has been found by those who treat these disabilities that feet withstand walking on pavements better if the sole of the shoe is thick and firm; that rubber and thin flexible shoes very commonly aggravate this disability. Other studies with motion-picture camera and electrical recording apparatus have attempted to determine the best type of heel and the general configuration of the shoe. The evidence so far obtained suggests that the following is the best type of shoe:

An oxford is the best style for giving support and for holding the foot. Orthopedists are agreed that no greater support is given by a high shoe or boot. The heel of the shoe should be 1 inch or less for men, not more than  $1\frac{1}{2}$  inches for women, and should have a wide base. It should not be pointed and narrow. The sole should have a straight inner border, since a narrowing at the toe leads to a deformity of the great toe joint, a crowding of the forepart of the foot, and eventual strain. The box should be fairly high, so that a small amount of flexion of the toes is possible. If the toes are pushed down, an atrophy of the lumbrical muscles, which hold up the so-called anterior arch, will result. The shoe should be at least  $\frac{1}{2}$  inch

longer than the great toe, since the foot lengthens when weight is borne. The width of the shoe should be such that in standing the leather presses against the sides of the foot comfortably. The vamp should be loose enough that the arch is not depressed when the shoe is laced snugly. It has been suggested that if the sole is cut in well on the inner side at the instep, more support will be given to the long arch; most shoes are made this way but the Reviewer does not have definite evidence on this point. For wear on hard floors and pavements, a thick stiff sole is most comfortable. Some manufacturers insert a thin plate of steel to add to the stiffness of the counter, but this is not essential. The heel of the shoe should be well-cupped, since the lower surface of the human heel is not a plane surface. The back of the shoe should come in to fit snugly just above the os calcis. This is the place where most shoes do not fit well, particularly in children. This is a frequent cause of blisters, and bursitis in this region, as well as being unsightly. There is no one perfect shoe. Most shoe manufacturers have co-operated in making good shoes to as great an extent as demand and fashion have permitted. The varying prices of shoes depend upon the quality of the leather used, less wear being expected from the cheaper ones.

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## DISLOCATIONS AND FRACTURES

By JOHN ROYAL MOORE, B.S., M.D.

### Amputations

**High Ligation of Femoral Vein in Amputation of Lower Extremity**—In a review of 171 cases of amputation, Veal<sup>8</sup> found the mortality was 39.1 per cent, a majority of deaths being due

to pulmonary complications. This mortality rate for amputation was high and out of proportion to other operative procedures.

After a study of the anatomy of the leg in relation to blood supply and of

TABLE I  
RESULTS OF TREATMENT IN 85 CASES OF FRESH COMPOUND FRACTURES

Results	Sulfanilamide Therapy			No Sulfanilamide		
	Cases			Cases		
	Number	Per Cent	Average Time (Months)	Number	Per Cent	Average Time (Months)
Not infected	25	71.4	3.1	33	66.0	2.7
Union	18	51.4		28	56.0	
Nonunion	4	11.4		3	6.0	
Incomplete	3	8.6		2	4.0	
Infected	10	28.6	2.7	14	28.0	5.0
Union	4	11.4		8	16.0	
Osteo	0	0.0		2	4.0	
Nonunion	3	8.6		0	0.0	
Amputation	3	8.6		2	4.0	
Incomplete	0	0.0		2	4.0	
Died . . .	0	0.0	0.0	3	6.0	6.0
Totals	35	100.0		50	100.0	

the autopsy findings in patients who had submitted to amputation, it was believed that the pulmonary complications could be explained on the basis of embolic phenomena. The femoral vein was devoid of tributaries up to the deep profunda in many specimens examined. This resulted in thrombosis up to the deep profunda and some extension of the thrombus into the junction of these 2 vessels. This was conducive to the formation of the emboli.

High ligation of the femoral vein just distal to the saphenofemoral junction was advised. Amputations following this procedure in 28 consecutive cases bore out the theory by the lowered mortality.

### Compound Fractures

**Treatment—Sulfanilamide and Internal Fixation**—Fifty-four cases were reviewed by Campbell and Smith<sup>9</sup> in which the patients received sulfanilamide as a prophylactic measure. These patients were divided into 3 groups:

(1) Fresh compound fracture; (2) old compound fractures with a previous infection; and (3) compound fractures with an active draining infection. In the first group from  $\frac{1}{2}$  to  $\frac{2}{3}$  ounce (15 to 20 Gm.) of sulfanilamide crystals were placed directly into the compound wound, and the wound was closed without drainage. After 24 hours, sulfanilamide was continued by mouth, 15 to 20 grains (1 to 1.3 Gm.) every 4 hours. For comparison, Campbell and Smith used a control group of 33 cases in which sulfanilamide was not employed. Table I gives the results of this study.

An analysis of Table I shows that the percentage of infections in the control group and in the sulfanilamide group was approximately the same. The average period of union, however, in the sulfanilamide group wherein infection developed was 2.7 months as compared with 5 months in the control group. This suggests that sulfanilamide is definitely instrumental in arresting infection.

TABLE II

Results	Mild Fractures		Moderate Fractures		Severe Fractures	
	No Internal Fixation	Internal Fixation	No Internal Fixation	Internal Fixation	No Internal Fixation	Internal Fixation
Not infected	8	6	0	5	6	
Union	6	4	0	4	4	
(Average time, months)	(3 6)	(2 4)		(3 5)	(3 0)	
Nonunion	0	2	0	1	1	
Too early	2	0	0	0	1	
Infected	0	1	1	4	4	
Union	0	1	0	1	2	
(Average time, months)	(1 0)			(4 0)	(3 0)	
Nonunion	0	0	1	2	0	
Amputation	0	0	0	1	1	
Gas gangrene	0	0	0	0	1	
Totals.	8	7	1	9	10	

Table II gives the results of treatment with sulfanilamide in mild, moderate, and severe fresh compound fractures

In old compound fractures with latent or potential infection, the authors found the following results

TABLE III

Results	Internal Fixation No Postoperative Infections		No Fixation No Postoperative Infections	
	Cases	Average Time	Cases	Average Time
Union	3	5 months	2	3 months
Too early	1		1	
Totals	4		3	

The authors reviewed 12 cases of compound fractures with active infection in which treatment with sulfanilamide was employed. The results were practically the same whether or not internal fixation was used. There was very little difference in the average period of union between those with and without fixation.

The authors believe that the evidence presented does not prove definitely that sulfanilamide either is or is not a preventive of infections in compound wounds, but that the present impression is favorable.

Key and Burford<sup>10</sup> experimented on 15 rabbits and 12 dogs to ascertain whether sulfanilamide crystals placed in the wound of a compound fracture after débridement would reduce the percentage of infections, or delay the healing of the fractures. Symmetrical fractures were produced in both forelegs, the right legs being pocked with crystals of sulfanilamide, while the left leg fractures were left alone. They concluded that from the x-ray appearance, the microscopic sections and the time of union, sulfanilamide tends to lessen the danger of infections and does not perceptibly interfere with union of the soft parts of the wound.

Estes<sup>11</sup> reports 25 open fractures treated with *Dakin's solution* for primary irrigation. Five of these were treated by packing wide open with vaseline gauze, 10 had complete closure of

the wound; 9 had the wound sutured and drained; and 1 had the Carrel-Dakin treatment. He concludes that antiseptics are of value in skin disinfection, but are seldom necessary in the treatment of the wound itself. An antiseptic would be an added safeguard in anaerobically or soil-contaminated wounds but that is all.

Cannaday<sup>12</sup> advocated the *primary closure of traumatic wounds*. The technic is as follows:

The routine application of a first aid sterile compress of gauze which may or may not be saturated with an antiseptic solution; thorough splinting of the part is absolutely necessary for satisfactory transportation of the patient. The method in general use for the cleaning up of a compound fracture includes the free use of *liquid green soap and warm water*. Shaving about the wound is followed by prolonged and thorough *irrigation of the laceration with* large amounts of *saline solution*. The skin about the laceration is painted with some *antiseptic*, the area is draped, and an extremely thorough but conservative *débridement* is done, including grossly contaminated bone which can be pared away by the use of the chisel or rongeur. If possible, the *fracture* is *reduced*, after which the skin wound is closed if it is practical to do so. In case there is much dead space or likelihood of an accumulation of serum, the *suturing* is done lightly in interrupted fashion so that any accumulation of fluid can drain out by seepage between the sutures. After a painstaking *débridement*, the wound is irrigated again with *warm saline* and a *cast* applied.

A review of *war fractures* treated by the *closed method* of reduction is given by Soulie and Linares<sup>13</sup>. They reported a total of 389 cases of war fractures treated by the closed method of reduc-

tion either immediately or delayed. The *indications* for the early closed treatment are (1) Reduction within 6 hours after the injury and (2) complete extirpation of all devitalized tissue with absolute certainty. Most of the fractures reported, however, were compound in nature, with extensive wounds. These cases were treated by the *delayed closed method* which consisted of *débridement*, saucerization, extraction of the foreign body and bone splinters, and the application of a plaster cast directly against the wound and skin without the interposition of dressing to the wound or cotton batting and without fenestration.

The authors report that there were no deaths and no amputations. The end-results for the 389 cases were:

Good	.	332	85.34%
Fair		40	10.28%
Poor	.	17	5.37%

Injuries to the soft parts around the fracture sites were found in 218 cases. The end-results were good in 206, fair in 9, and poor in 3 of these cases. Ninety-three had moderate fractures and 78 had severe fractures. The results for the second group were good in 71, fair in 14, and poor in 8. The last group—the severe type of fracture—the results were good in 55, fair in 17, and poor in 6 cases.

In compound war fractures the *delayed closed treatment* is indicated, using the *Orr treatment* to allow filling-up of large cavities which resulted from the shrapnel, or to allow the extraction of sequestra. This method is contraindicated in (1) the presence of a vascular lesion; (2) in the case in which it is not certain that all devitalized tissue has been completely excised, and (3) in the case in which simple *débridement* has been done or effective intervention must be delayed. Reduction of the fracture must be done before the application of

TABLE II

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	No Internal Fixation	Internal Fixation	No Internal Fixation	Internal Fixation	No Internal Fixation
Not infected	8	6	0	5	6
Union	6	4	0	4	4
(Average time, months)	(3.6)	(2.4)		(3.5)	(3.0)
Nonunion	0	2	0	1	1
Too early	2	0	0	0	1
Infected	0	1	1	4	4
Union	0	1	0	1	2
(Average time, months)	(1.0)			(4.0)	(3.0)
Nonunion	0	0	1	2	0
Amputation	0	0	0	1	1
Gas gangrene	0	0	0	0	1
Totals	8	7	1	9	10

Table II gives the results of treatment with sulfanilamide in mild, moderate, and severe fresh compound fractures.

In old compound fractures with latent or potential infection, the authors found the following results:

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Estes<sup>11</sup> reports 25 open fractures treated with *Dakin's solution* for primary irrigation. Five of these were treated by packing wide open with vaseline gauze; 10 had complete closure of

of the 36 patients were treated by this operative technic. A Langenbeck incision is made and sufficient bone from the lower end of the humerus and the upper end of the ulna is excised to produce a gap of at least  $1\frac{1}{2}$  inches. The bones are shaped to resemble the normal ar-

of a week the stitches are removed, at the end of a fortnight the Kirschner wire is removed, and active flexion with slight support is encouraged. On the first day active flexion to  $160^\circ$  is usually obtained. To prevent effusion as a result of this movement, the elbow is sup-

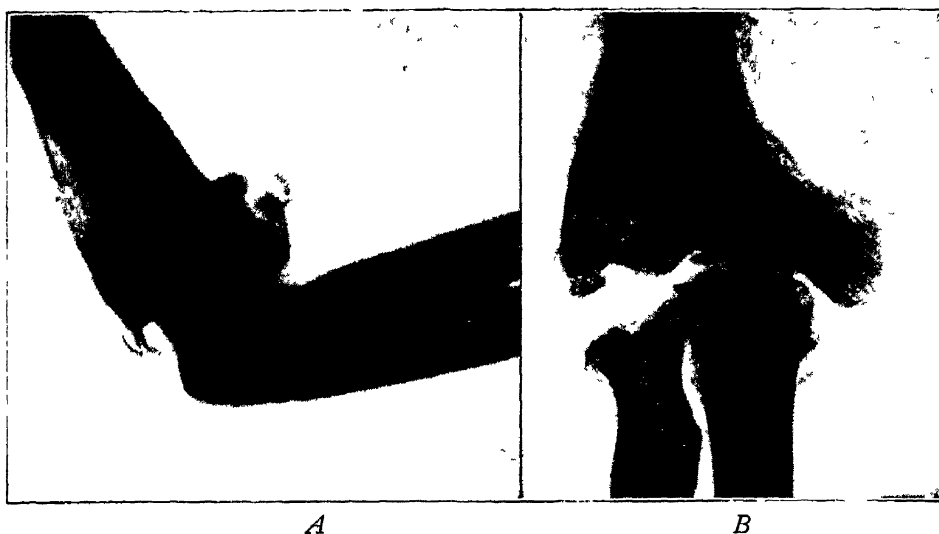


Fig. 2—Lateral and anteroposterior roentgenograms 3 years after excision. (Kini. J. Bone and Joint Surg.)



Fig. 3—Photographs showing weight-bearing capacity of elbow with arm in abduction at shoulder and with forearm in supination. (Kini. J. Bone and Joint Surg.)

ticular ends and are smoothed by a file. To keep the bone ends apart, skeletal traction from the lower end of the radius and of the ulna is obtained by Kirschner wire. After a firm bandage has been applied to the elbow to prevent effusion, the limb is put in extension in a Thomas arm splint for a fortnight. At the end

ported in a cast. This method of active flexion is repeated from day to day until flexion from  $45$  to  $50^\circ$  is obtained. In about 2 months' time the power to flex and to extend the elbow against resistance is easily restored.

The results obtained have been very satisfactory.



**External Lateral Dislocation of Elbow**—This is rare type of elbow injury reported by Griesemer.<sup>16</sup>

**Physical Signs**—Forearm in a position between extension and right angle

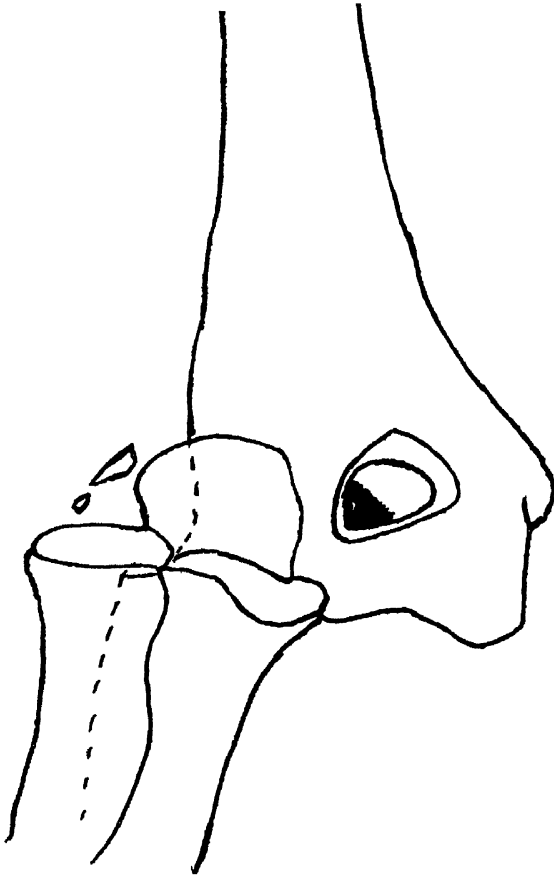


Fig. 4—Diagrammatic representation (Griesemer. Am J. Surg.)

flexion. Pronation of the forearm and right angle flexion. Pronation of the forearm is common and is due to pressure under the muscles which take attachment from the external condyle and are made tense. The internal condyle is made prominent, the skin being made very tense over it and it may have a rough edge if the epitrochlea has been avulsed. There is increased protuberance of the olecranon, because the ridge of the sigmoid cavity interlocks in the deep groove between the outer margin of the trochlear surface and the capitellum. The external condyle is usually

not prominent but may be identified by making strong pressure above the head of the radius, behind the extensor muscles. The very definite widening of the transverse diameter of the joint is the most prominent sign. The triceps tendon stands out as a very tense band.

**Treatment**—*Closed reduction* at once. Forearm manipulated into strong pronation, at the same time extending it and continuing with lateral flexion and supination. After reposition the arm is put into acute flexion and held there by a *posterior moulded plaster splint* from midhumerus to the distal ends of the metacarpals. If closed reduction fails, *open operation* should be performed at once.



Fig. 5—Lateral view, showing epitrochlea displaced into olecranon fossa of humerus. (Griesemer. Am. J. Surg.)

Six cases were reported, all good results.

**Simple Anterior Dislocation of Elbow Joint with Rupture of the Brachial Artery**—In describing a case,



Fig. 6—*A*, Anteroposterior view, showing evidence of union of epitrochlea to humerus and reparative process of external condyle, with thickening of adjacent periosteum. (Dec. 2, 1935.)  
*B*, Same case, showing further union of epitrochlea. (Mar 9, 1936) (Griesemer: Am. J Surg)

### Supracondylar Fractures of the Femur Treated by skeletal traction From the crest of the Tibia

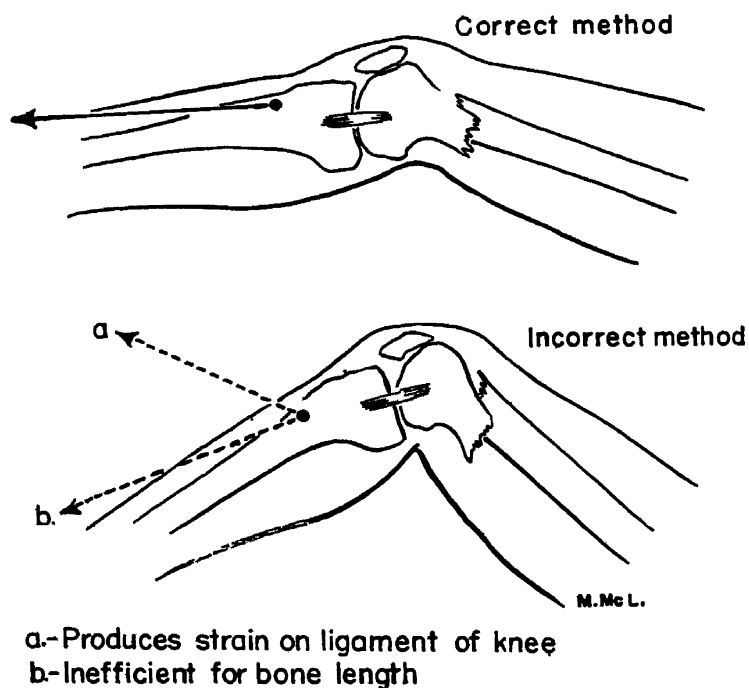


Fig. 7—Correct and incorrect methods of traction. (Van Gorder: Am. J. Surg.)

Jackson<sup>17</sup> states that this condition should always be suspected in injuries of the elbow joint, and especially in dislocations accompanied by absence of the radial pulse and change in color of the hand. Immediate diagnosis and surgical interference are necessary to save the extremity. Jackson *anastomosed* the *artery* and an excellent result followed, with only slight restriction in extension of the elbow.

### Femur

**Fracture of Femur**—Van Gorder<sup>18</sup> showed what happened when *skeletal traction* was used ordinarily in civilian patients by a combined group of general surgeons and orthopedic surgeons in Boston City Hospital. Fifty-eight fractures were reported, 51 of the fractures being simple and 7 were compound. Ice tongs were used in 36 cases; Kirschner wires in 18; and Steinmann pins in 4 cases.

In 14 cases of the 58, skeletal traction was given up during the course of the treatment because of:

Unsuccessful reduction . . . . .	7 cases
Nonunion . . . . .	3 cases
Compound fracture amputation..	1 case
Delirium tremens . . . . .	1 case
Operator's choice . . . . .	1 case
Death . . . . .	1 case

14 cases

Van Gorder summarizes his 58 femoral shaft fractures by saying:

1. The average hospital stay of the patients was 11½ weeks.
2. There were 3 cases of nonunion.
3. Thirteen cases, or 31 per cent, in which leg length was measured a year or more after treatment, showed an average shortening of ¾ inch.
4. Knee-joint motion was limited in 11 of the 43 recorded cases—average limitation being 76.5°.

5. The average length of time elapsed between the injury and the date when the patients returned to work was 7¼ months.

6. The end-results rating of the 58 patients showed 57 per cent excellent, 30 per cent good, 5 per cent fair and 8 per cent poor.

Intertrochanteric Fracture  
With external rotation of shaft  
Treated by skeletal traction

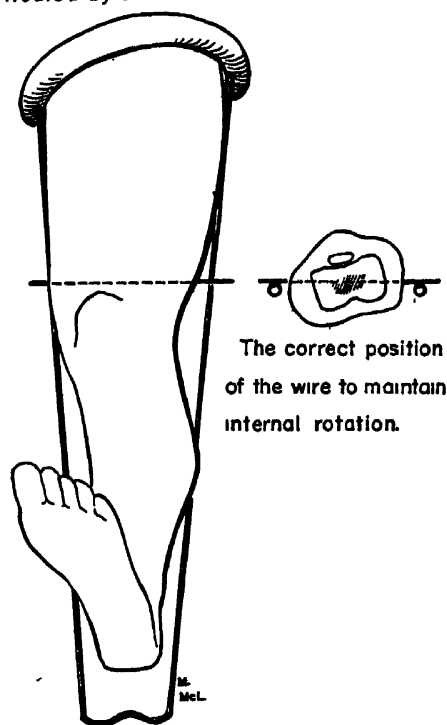


Fig. 8  
(Van Gorder: Am. J. Surg.)

This is a good cross section study representing the *average* end-results that might be expected from the use of skeletal traction in the treatment of fractures of the femur.

Dunlop<sup>19</sup> believes that the *Russell traction* is well adapted for the initial treatment of all types of fractures of the femur from intertrochanteric down to the condyles. He reported 741 cases. Russell traction is *contraindicated* in femoral neck fractures if the leg of the same side is fractured below the knee,

if the foot on the same side is injured, or if there are extensive skin injuries.

Darrach<sup>20</sup> reported 60 cases of fractured shaft of femur treated by *open*

was no shortening in 53 cases and all 60 patients had solid bony union. There were 2 deaths, neither attributable to the plating procedure.

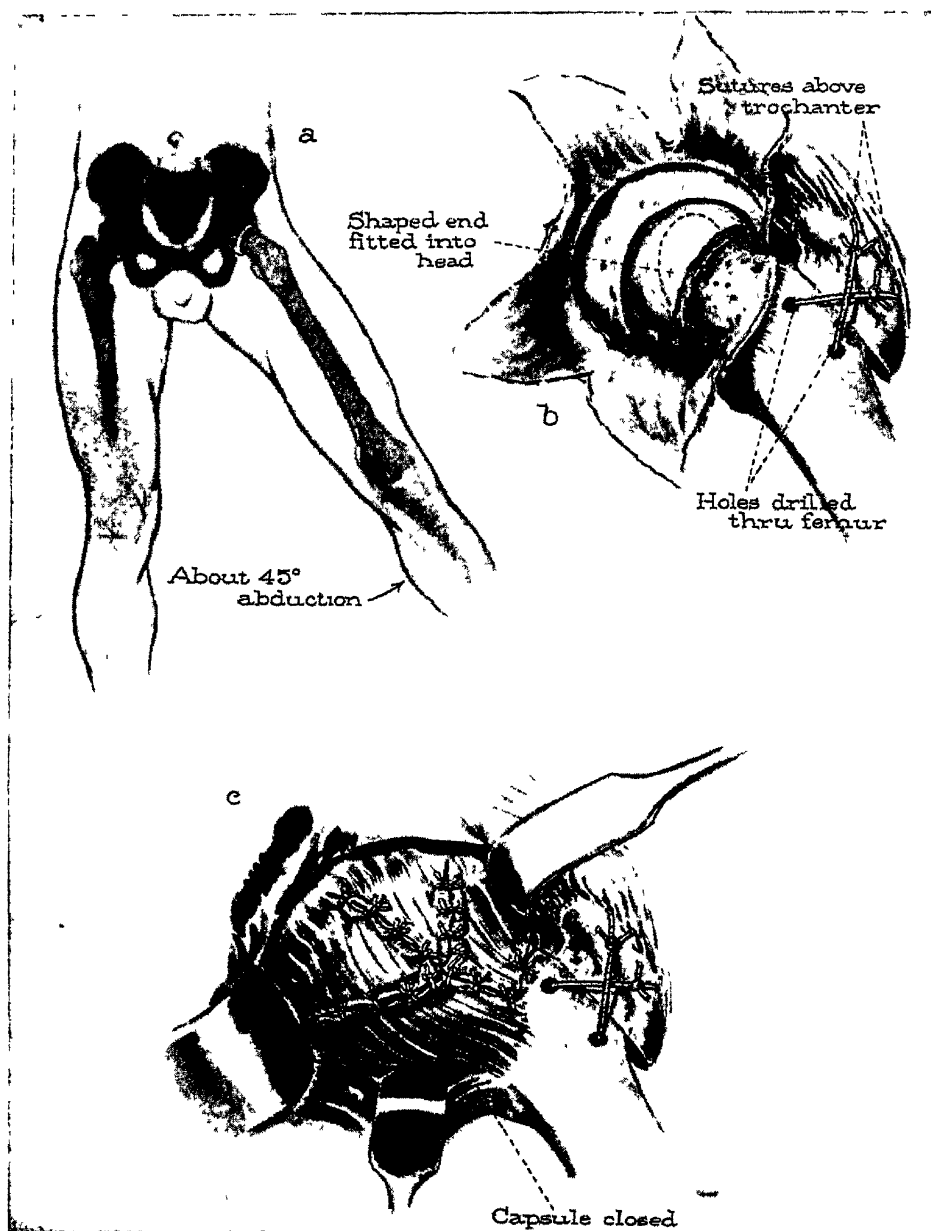


Fig. 9—Third stage of operation. Rounded end of shaft fitted into hollowed-out head; trochanter replaced downward and outward from original location. *a*, Position of shaft in head at completion of operation; *b*, head hollowed out in form of a parabola, with end of shaft fitted into it and trochanter attached to upper end of femur below and lateral to its former position; *c*, closure of capsule. (Magnuson. "Fractures," J. B. Lippincott Co., Phila.)

**reduction and fixation.** In 7 of these the plates broke; in 8, the screws were loosened with angulation; in 16, the plates and screws were removed. There

The problem of the *ununion* fracture of the neck of the femur was discussed by Magnuson,<sup>21</sup> who reported 59 cases in which 41 had the *Magnuson opera-*

tion (a modification of the Brackett), 7 had the *Whitman reconstruction*, 5 had *high intratrochanteric osteotomy*, 2 had *Colonnas*, and 4 patients had miscellaneous operations. The ages ranged from 34 to 84 years with the average at 57 years. Females predominated 3 to 1. The average shortening before operation was 1.5 inches, after operation  $\frac{3}{4}$  inch.

**Results**—41 cases—28 cases, good; no pain, good function; 2 cases, death; 6 cases, poor results, shaft having slipped out of the head with lack of weight-bearing stability; 1 case, Whitman; 1 case, high osteotomy; 1 case, head collapsed and gradually disintegrated; 1 case, questionable; 1 case, no report.

**Reconstruction in Femoral Neck Fractures**—Hermann<sup>22</sup> reported 23 cases.

(1) COLONNA METHOD, 10 cases; 7 successful, 3 unsuccessful.

**Finding**—Bed and hospital confinement was shorter than by any of the other methods used. The average was 6 weeks in bed with another 2 weeks up and about the ward. Average shortening was a scant inch. Internal and external rotation at the hip were limited; abduction, 25 to 45°; adduction, 20 to 25°; flexion, good; extension, normal.

(2) MAGNUSON OPERATION, 5 cases. This combines the best features of the Whitman and Brackett operations, and requires a very careful selection of cases. It should not be considered in cases complicated by arthritic changes or in cases in which the head of the femur is dead.

**Results**—Successful, 3 cases; unsuccessful, 2 (death).

(3) BONE-GRAFTING AND ALLIED METHODS, 3 cases—all successful. Non-united fractures were of 6½ to 8 months' duration. The femoral heads were all in good condition and a fair amount of

femoral neck remained. All patients had normal range of function, better than the Magnuson cases.

(4) OSTEOTOMY PROCEDURE, 2 cases. McMurray technic. Period of fixation and hospitalization is too prolonged for such poor surgical risks. Both patients died sometime after operation.

(5) HIP FUSION, 3 cases. Used in cases of nonunion in which definite arthritic or other joint changes were shown.

**Results**—Successful, 2; failure, 1.

**Internal Fixation**—Rankin<sup>23</sup> concludes from a review of the literature that the treatment of fractures of the neck of the femur by closed methods does not give satisfactory results. The use of internal fixation decreases the financial strain on the patient, lessens the period of hospitalization, lowers the mortality and very definitely improves the end-results.

He reports 25 cases, 8 trochanteric fractures, 17 intracapsular fractures, treated by the *Smith-Peterson* and the *Moore nails*. Of the 17 intracapsular cases, there were 2 deaths and 2 nonunion with dead head, 13 solid bony union, or 76 per cent. All trochanteric fractures had union, or 100 per cent. Age incidence, 39 to 95 years.

**Ununited Fractures**—Ununited fractures may be divided into 2 classes, according to Henderson,<sup>24</sup> *i. e.*, (1) those in which bones are merely delayed in uniting; (2) those in which the fragments are in a fixed state of nonunion and evidence of an attempt at consolidation is to be seen.

In a series of 583 patients with ununited fractures treated by *bone-grafting operation*, the relation incidence as to the bones involved was as follows: Tibia, 233; humerus, 100; femur, 100; radius, 70; radius and ulna, 44; ulna, 30; clavicle, 5; metatarsal, 1. The end-

results in 530 cases were as follows: Union of tibia, 94 per cent, radius, 93 per cent, ulna, 89 per cent; humerus, 86 per cent, radius and ulna, 85 per cent, femur, 78 per cent

How can *delayed union* be *distinguished from nonunion*? In the typical case of nonunion, pain and tenderness are absent. The x-rays show the bone ends to be clean-cut and rounded. They lack an irregular, somewhat fuzzy excessive formation of callus so often seen in delayed union. Any *open operation* which consists of freely dissecting away fibrous tissue from about and between the bone ends, freshening and fitting them together, and providing internal fixation by metal devices and external fixation with *casts* or *splints*, will bring about union of many ununited fractures. The *autogenous bone graft* gives best results.

Operations should not be undertaken in the face of draining sinuses or of evidence of inflammation. The *bone graft* should be as large as possible and must be held firmly clamped to the fragments. Multiple chips of bone packed about the site of fracture are of great aid. Fractures of the neck of the femur can be dealt with successfully without arthrotomy in cases in which fibrous union has occurred. The method consists in overcoming the shortening with traction, securing anatomic alignment, and inserting a large piece of autogenous bone, such as a fibular segment of such length that it extends from the trochanter well into the head. Fractures of the lower end of the humerus are the most difficult of all humeral fractures to deal with and are best treated by the "onlay massive" graft.

### Humerus

**Supracondylar "T" Fractures**—Eight cases of supracondylar "T" fractures have been treated by open reduc-

tion and the results recorded by Van Gorder.<sup>25</sup> Because of the interposition of soft parts, wide separation of the condyles, or neglect, these cases had to have the following procedure:

"The patient lies face down on the operating table with his arm flexed over a well-padded arm board. A small-sized

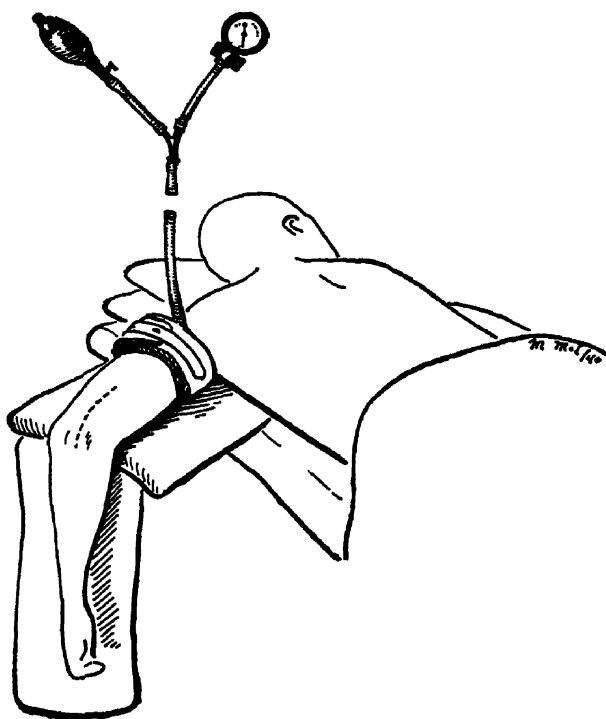


Fig 10—Shows position of patient on operating table with tourniquet in place and line of incision (Van Gorder J Bone and Joint Surg)

pneumatic tourniquet facilitates the operative technic and is considered essential. A posterior midline incision is made through the skin, starting 5 inches above the olecranon and extending downward to 1 inch below its tip (Fig 10). The skin and subcutaneous layers are dissected widely on both sides to expose the lower portion of the triceps muscle, its insertion, and expansions. The ulnar nerve is then isolated and gently retracted.

"The superficial fascia covering the triceps muscle is cut in the shape of a long tongue, the apex of which is about

4 inches above the olecranon and the base of which widens out at the joint line to the outer borders of both humeral condyles. When making this fascial incision, the operator should be careful to



Fig. 11—Incision deepened through triceps muscle and continued outward and inward to tips of both condyles, dividing completely muscle expansions, but avoiding ulnar nerve. (Van Gorder: J. Bone and Joint Surg.)

keep his knife blade strictly within the confines of the fascia itself, in order to preserve a strong fascial edge adjacent to the muscle, which is utilized later for suturing in repair of the wound.

“Beginning at the apex of this marked-out tongue of fascia, dissection is directed toward the elbow-joint, steadily deepening the plane of dissection as the joint line is approached. Thus, as the tongue of tissue is raised from its bed, the apex portion will contain only

fascia; the midportion, fascia and a superficial layer of muscle; while, as the dissection proceeds and deepens, the base of the tongue will finally include the entire thickness of the triceps muscle along with its tendon. As the dissection lines curve outward on both sides to the humeral condyles, the lateral expansions of the triceps muscle are completely divided down to bone, care being taken not to injure the ulnar nerve (Fig. 11).

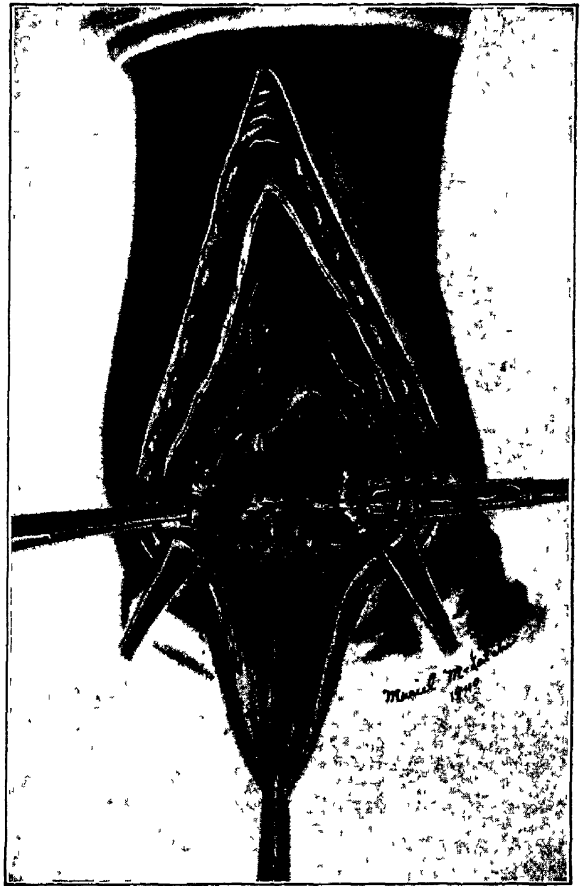


Fig. 12—Fractured bone fragments shown fixed in position by steel plates and transfixion bolt. (Van Gorder: J. Bone and Joint Surg.)

“The dissected tongue of fascia and muscle is now entirely free with the exception of its base, which remains firmly attached to the olecranon and fascial prolongations. It is now folded backward on itself, exposing what re-

mains of the deepest portions of the triceps muscle that overlies the bone. Another longitudinal midline incision, deepened down through the periosteum, separates these remaining muscle fibers and allows them to be retracted with the periosteum to either side. In this manner, the entire posterior surface of the lower end of the humerus, including its mesial and lateral aspects, as well as the joint line, is brought into full view.

## Tendons

### Dislocation of Extensor Tendon—

A case of dislocation of the extensor tendon at the third metacarpophalangeal joint is reported by Straus.<sup>26</sup> Fig. 13, *A*, shows the apparent normal relations of the extensor tendon of the middle finger when in full extension; *B*, the extensor tendon of the middle finger beginning to slip to the ulnar side of the third metacarpal, with the finger in 45° flexion; *C*, showing ulnar deviation of middle finger, upon complete flexion, with extensor tendon slipped entirely to ulnar side of third metacarpal, with the finger in 45° flexion;



Fig. 13—*A*, Apparent normal relations of extensor tendon of middle finger when in full extension. *B*, Showing extensor tendon of middle finger beginning to slip to ulnar side of third metacarpal, with finger in 45° flexion. *C*, Showing ulnar deviation of middle finger, upon complete flexion, with extensor tendon slipped entirely to ulnar side of third metacarpal (Straus: Ann. Surg.)

After reduction and fixation of the fracture have been accomplished (Fig. 12), the periosteum and the deepest layer of the triceps muscle are approximated in the midline with interrupted sutures, after which the fascial tongue is replaced in its bed and sutured securely to its corresponding tissue layers, which were carefully preserved for this purpose. The ulnar nerve should be seen lying in a bed of uninjured muscle before closure of the skin."

In 5 of the cases the results were excellent, 1 was a complete failure, and, in 2 cases the results were "poor."

and *C*, the ulnar deviation of the middle finger with the extensor tendon slipped entirely to the ulnar side of the third metacarpal.

The dislocation may be the result of disease or trauma. There is immediate disturbance of function and there is swelling of the dorsum of the hand, the interference of extension being permanent unless it is repaired. The dislocation may be the result of a direct blow on the metacarpophalangeal joint which tears the extensor tendon loose from its normal bed; or may be due to indirect violence caused by contraction of the ex-



tensor tendon against resistance; or by external force causing flexion of the finger against muscular resistance.

**Treatment**—The operative exploration of the tendon was as follows: Under

don was found to be torn and separated into a "V" (Fig. 14, A). This allowed the intact lateral one-half of the tendon to slip toward the ulnar side of the metacarpal head. There was no vinculum

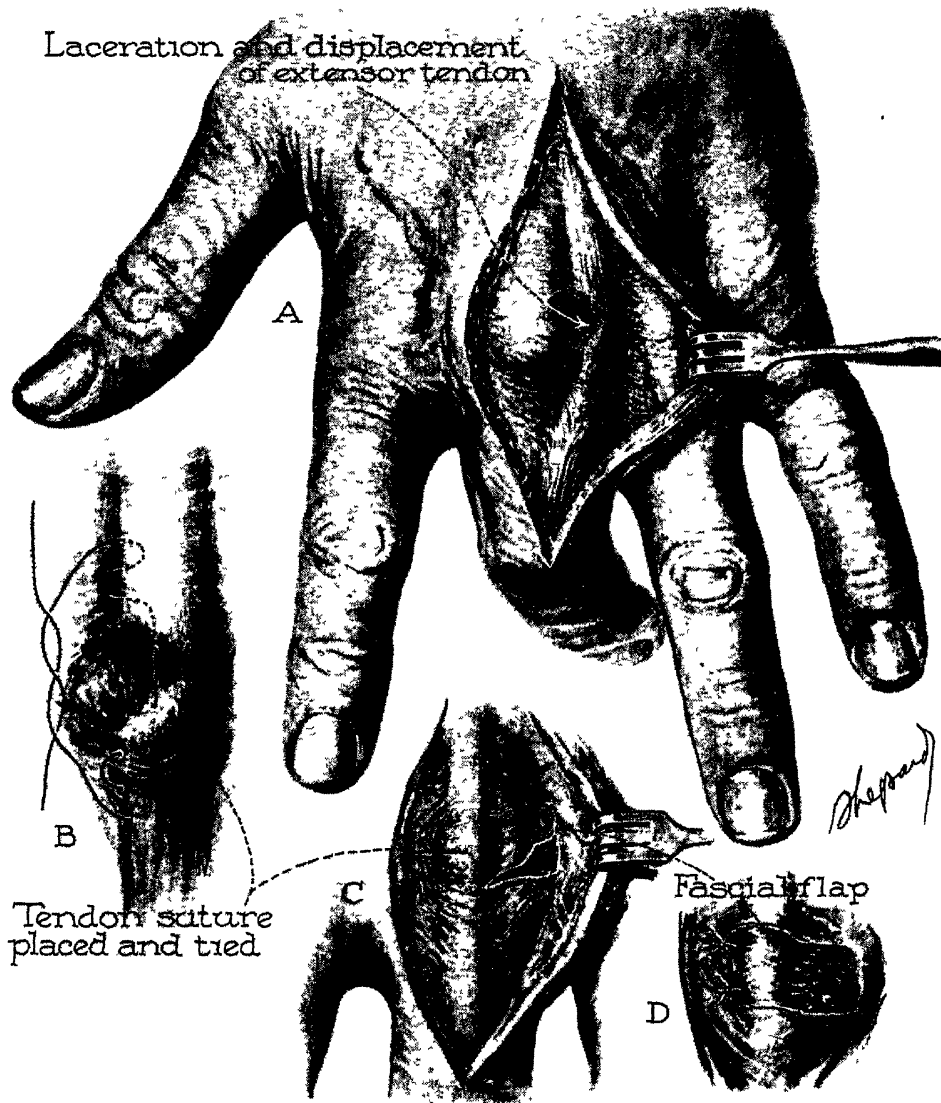


Fig. 14—Drawing illustrating: A, The "V" tear in extensor tendon; intact vinculum between extensor tendons of ring and middle fingers; absence of vinculum between extensor tendons of index and middle fingers. B, C and D, Operative procedures employed in effecting repair. (Straus. Ann. Surg.)

local anesthesia a longitudinal incision was made over the metacarpophalangeal joint of the middle finger and the extensor tendon was exposed. At the level of the metacarpophalangeal joint, the medial one-half of the flat extensor ten-

don was found to be torn and separated into a "V" (Fig. 14, A). This allowed the intact lateral one-half of the tendon to slip toward the ulnar side of the metacarpal head. There was no vinculum

fect in the tendon was repaired by silk sutures (Fig. 14, B). A rectangular flap of connective tissue was turned up from the ulnar side of the tendon (Fig. 14, C) and sutured over the tendon to the soft tissue on the radial side of the tendon (Fig. 14, D). The skin was closed over this with interrupted silk sutures and a palmar splint applied. Eleven days later the wound was healed. Flexion and extension of the middle finger were normal and there was no luxation of the tendon in any position. One year later the condition was unchanged.

### Wrist

**The Carpus, with Reference to the Fractured Navicular Bone**—An adequate knowledge of the relationship of the carpal bones is necessary for making an adequate diagnosis of injuries to the above structures. Injuries to the carpal bones, with 1 or 2 exceptions, practically always heal when they are reduced properly and immobilized for a short time. The frequent exception to this rule is a fracture of the carpal navicular bone. Cave<sup>27</sup> reviewed some 4500 fracture cases treated at the Massachusetts General Hospital. Approximately 2 per cent were fractures or dislocations of the carpus. These fractures and dislocations are extremely important injuries because of the frequently disabled hands they produce. The author reported 110 carpal injuries with fracture of the navicular bone in 68 cases. He found this type of injury to be more frequent in the male sex, especially young adults who were exposed to severe trauma. Cave divides the cases into 4 types:

**Type 1:** The fracture occurring in the central or wrist portion.

**Type 2:** The fracture occurring at the junction of the proximal and the middle thirds.

**Type 3:** The fracture occurring at the tubercle of the bone.

**Type 4:** Comminuted fracture of the navicular bone.

**Treatment**—In the treatment of all fresh fractures of the carpal navicular bone, of fractures through the midportion, and of fractures at the junction of the proximal and the middle third (whether partial or complete), early and complete *immobilization* of the thumb, the hand, and the lower two-thirds of the forearm should be carried out. It is ideal to immobilize the thumb completely. The wrist should be 30° dorsiflexed and there should be 15° radial deviation. The immobilization period is 12 weeks.

Type 3 fractures always heal, for they are largely extra-articular and the blood supply to both fragments is maintained.

Type 4 fractures are best treated by *primary excision of the entire navicular bone* because of the danger of traumatic arthritis.

Cavé described the various methods of operative treatment for nonunion of the fractured bone, *i. e.*, excision of 1 fragment, excision of the entire navicular bone, drilling, and the autogenous bone graft. He believes that the introduction of an *autogenous bone graft introduced through a drill hole in the bone* followed by prolonged *fixation in plaster* produces the best results.

**Fracture of the Carpal Scaphoid**—Fracture of the carpal scaphoid was reported by Thorndike and Garrey<sup>28</sup> who advocated prolonged *immobilization with the wrist in extreme extension*. They reported 5 solid bony unions out of 6 cases treated by the above method.

**Colles' Fractures**—In a discussion of Colles' fracture, Mayer<sup>29</sup> reported 63 cases. "The results of Colles' fractures treated by present methods are extremely disappointing, redisplacement

TABLE IV

Reduction	Redisplacement	Pronation Plaster	Other Plaster	Results
Perfect	None	7 (64%)	5 (24%)	Perfect
	Slight	2 (36%)	10 (48%)	Good
	Severe	0 (0)	6 (28%)	Fair
Imperfect	None	7 (77%)	5 (20%)	Good
	Slight	2 (23%)	15 (60%)	Fair
	Severe	0	5 (20%)	Bad
Bad	None	0	0	Bad
	Worse	0	2 (100%)	

being exceedingly common even after perfect reduction. An important part of the displacement in most cases is a rotation of the lower radial fragment into supination, but this usually passes unrecognized." Fifty-three cases showed a supination-twist in the original x-ray.

Smith-Petersen<sup>30</sup> devised a new approach to the wrist-joint which may be

cision of this type results in 2 flaps, which are easily retracted. Since the incision is over the ulnar process of the wrist, the resulting scar is out of sight most of the time. By a division of the subcutaneous fat and fascia, the ulnar periosteum is exposed and incised. Following an oblique osteotomy, the distal inch or so of the ulna is removed, ex-

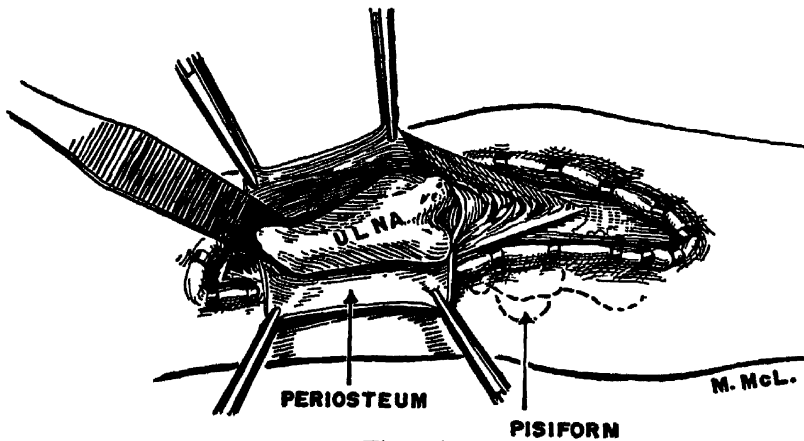


Fig. 15.  
(Smith-Petersen: J. Bone and Joint Surg.)

applied to any condition demanding exposure of the proximal or of the distal rows of carpal bones.

"The incision starts 2 or 2½ inches above the ulnar styloid, running parallel with the ulna to a point just distal to the styloid; it then curves anteriorly in the direction of the proximal end of the fifth metacarpal; the distal portion runs parallel with this bone for a distance of approximately 1 inch. A bayonet in-

posing the ulnar aspect of the radius. The capsule and ligaments are reflected from the radius along with the periosteum of the latter, exposing the radiocarpal joint. The same procedure is carried out distally, reflecting capsule and ligaments from the carpus. The increased mobility thus obtained facilitates the complete removal of the cartilage from the radius and the carpus. With the hands in the optimum position of

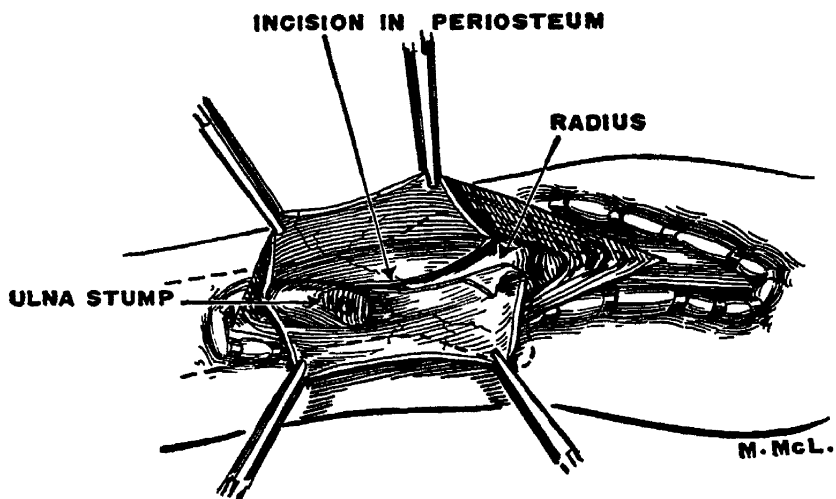


Fig 16  
(Smith-Petersen: J Bone and Joint Surg.)

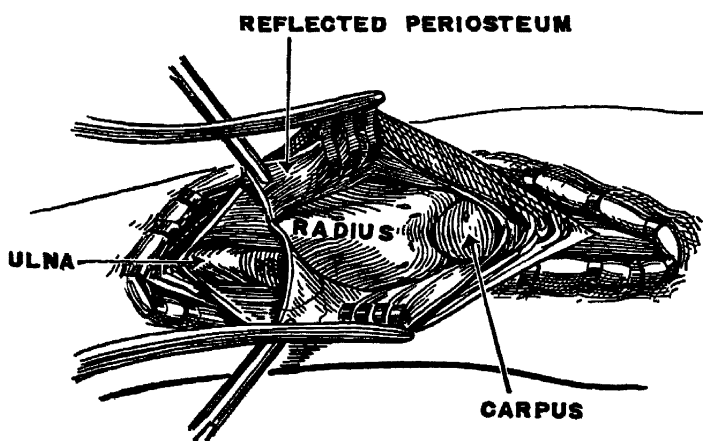


Fig 17.  
(Smith-Petersen: J. Bone and Joint Surg.)

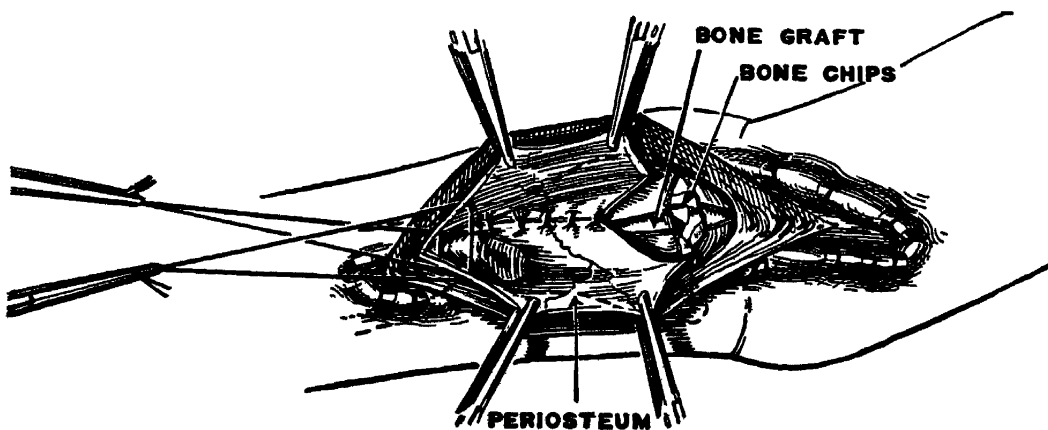


Fig. 18.  
(Smith-Petersen: J. Bone and Joint Surg.)

dorsiflexion, slots are cut in the radius and the carpus, into which the graft is sunk."

Figs. 15, 16, 17 and 18 show the new approach to the wrist.

### Clay-Shoveler's Fracture

McKellar Hall<sup>31</sup> calls attention to the fracture of one or more spinous process of

the base of the neck between the shoulders. The pain complained of between the shoulders was nearly always to 1 side of the midline, sometimes beneath 1 scapula. It was accentuated by stretching the arms and attempting to pull or lift anything. Signs at examination were tenderness of the spinous process and along the course of the rhomboid mus-

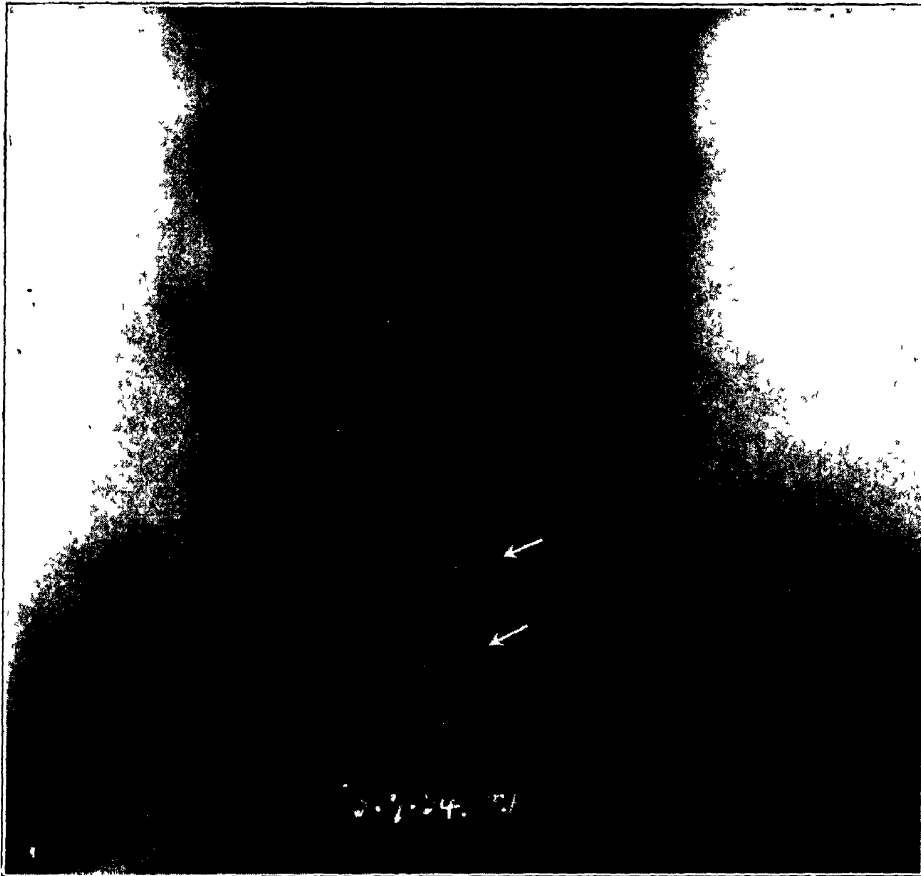


Fig 19—Before operation Fracture of spinous process of seventh cervical and first thoracic vertebrae, showing downward displacement, visible in anteroposterior film as well as in lateral film. (McKellar Hall: J. Bone and Joint Surg.)

the lower cervical or upper thoracic vertebrae which occurred in relief workers engaged in shoveling. In Western Australia, the term "clay-shoveler's fracture" has been attached to this condition. A frequent history in such cases is that of tossing up a shovel full of dirt and having it stick to the shovel with the result of a sudden, sharp snap at

cles on 1 side. Sometimes mobility of the affected spinous process could be detected. On active contraction or passive stretching of the rhomboid or trapezius, pain was invariable. Flexion of the head caused pain. The diagnosis was frequently missed, as the lesion was contributed to muscle strain and it was difficult to get good roentgenological

pictures of the involved spinous processes (Figs 19 and 20)

*Treatment* consisted of the immediate **removal of the fractured spinous processes**. In those cases of long standing, the success of this operation was

variable. The author explained that the lesion occurred mainly in relief workers who were happy to accentuate their disabilities. A long-standing case, therefore, was more reluctant to respond to any therapy.



Fig 20—Before operation. Lateral view. Fracture of spinous process of first thoracic vertebra is not visible in print, but can be seen in anteroposterior view (Fig 19) (McKellar Hall J Bone and Joint Surg.)

## DISEASES OF BONES AND JOINTS

By JESSE T. NICHOLSON, M.D.

### Changes in Bones and Joints Resulting from Interruption of Circulation

Phemister<sup>32</sup> presents pathologic and roentgenological aspects of necrotic bone produced by traumas of fracture, dislocation or operation. Particularly in fractures of the shaft there is devitaliza-

tion from the injury of the circulation at the fragment ends. The necrotic bone undergoes replacement by new bone and does not interfere with the union. Where there is massive splinter formation there may be extensive necrosis of bone. This necrotic bone undergoes creeping replacement by the new bone. In some

cases it is a factor in the causation of nonunion.

Complete severance of vascular connection, particularly in fractures bordering on joints as in the neck of the femur, the carpal navicular bone and the astragalus, results in the necrosis of the articular fragment (Figs. 21, 22, 23).

is complete. If the stress and strain of use and weight bearing is started early, the necrotic bone shell collapses and the joints become deformed. The poor functional results following traumatic dislocation of the hip, which previously were attributed to chronic arthritis, could be explained on the basis of trau-

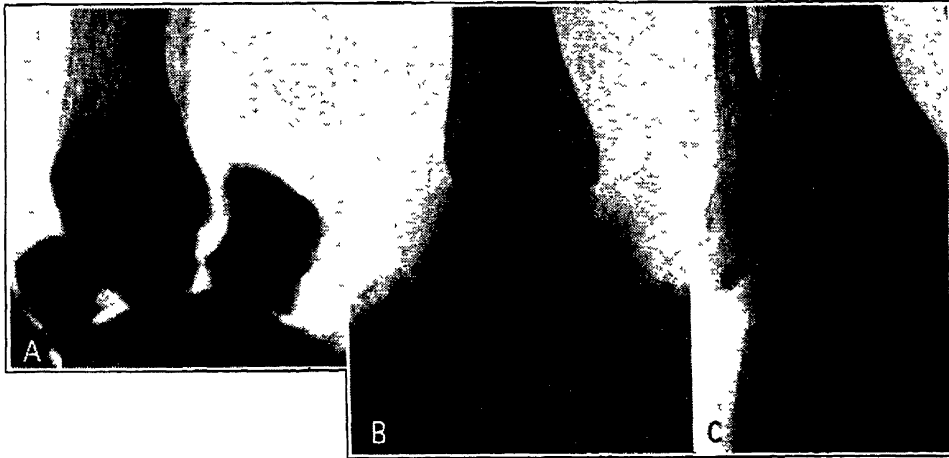


Fig. 21—*A*, Fresh fracture of neck of astragalus with posterior dislocation of body. Operative reduction followed. *B* and *C*, Condition 1 year and 19 days later. Fracture ununited and entire astragalus denser than surrounding atrophied bones, indicating necrosis (Phemister: Arch Surg)

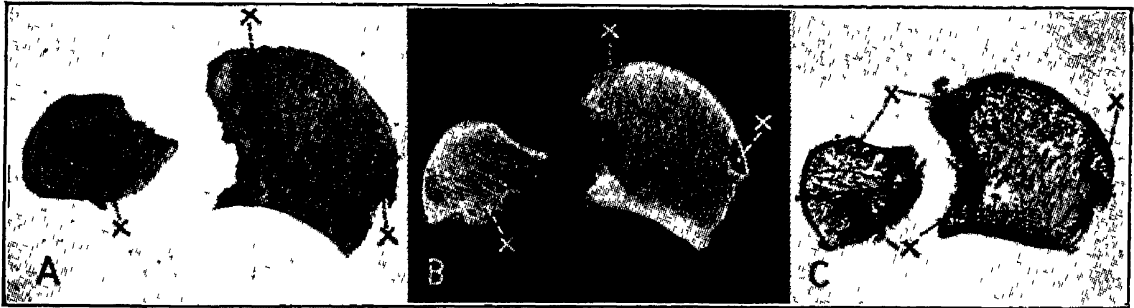


Fig. 22 (Case 3)—*A*, Photograph of cut and fractured surfaces; *B*, roentgenogram of slices; and *C*, microscopic sections of 2 dead fragments excised 15 months after injury. Fibrous invasion and partial creeping substitution indicated by *x* in lower half and upper margin of head and neck, in anterior margin along fracture surface and in posterior superior part of body. (Phemister: Arch. Surg.)

The articular cartilage of the joint fragment undergoes nutritional disturbance which contributes to the development of arthritis deformans and osteo-cartilaginous loose bodies. A fracture after union must be protected from stress and strain, particularly weight bearing, until the new bone replacement

matic injury to the blood supply of the head followed by necrosis. Following reduction of the dislocation, there is a period of months to a year of freedom from symptoms and a normal x-ray picture; then there is a gradual progression of weakness, stiffness and pain; then x-rays reveal the changes. In 42 cases

of dislocation in the adult, the joint was markedly deformed and the functional result was poor. Following dislocations in 8 children there was transformation of the head in each case, followed by a good functional result (Fig. 24). It is

ease (osteosclerosis fragilis generalisata). One child died on the ninth day of life; the other had been blind at birth but the disease was not discovered until the age of  $4\frac{1}{2}$  years. There was no hereditary history in these cases as has

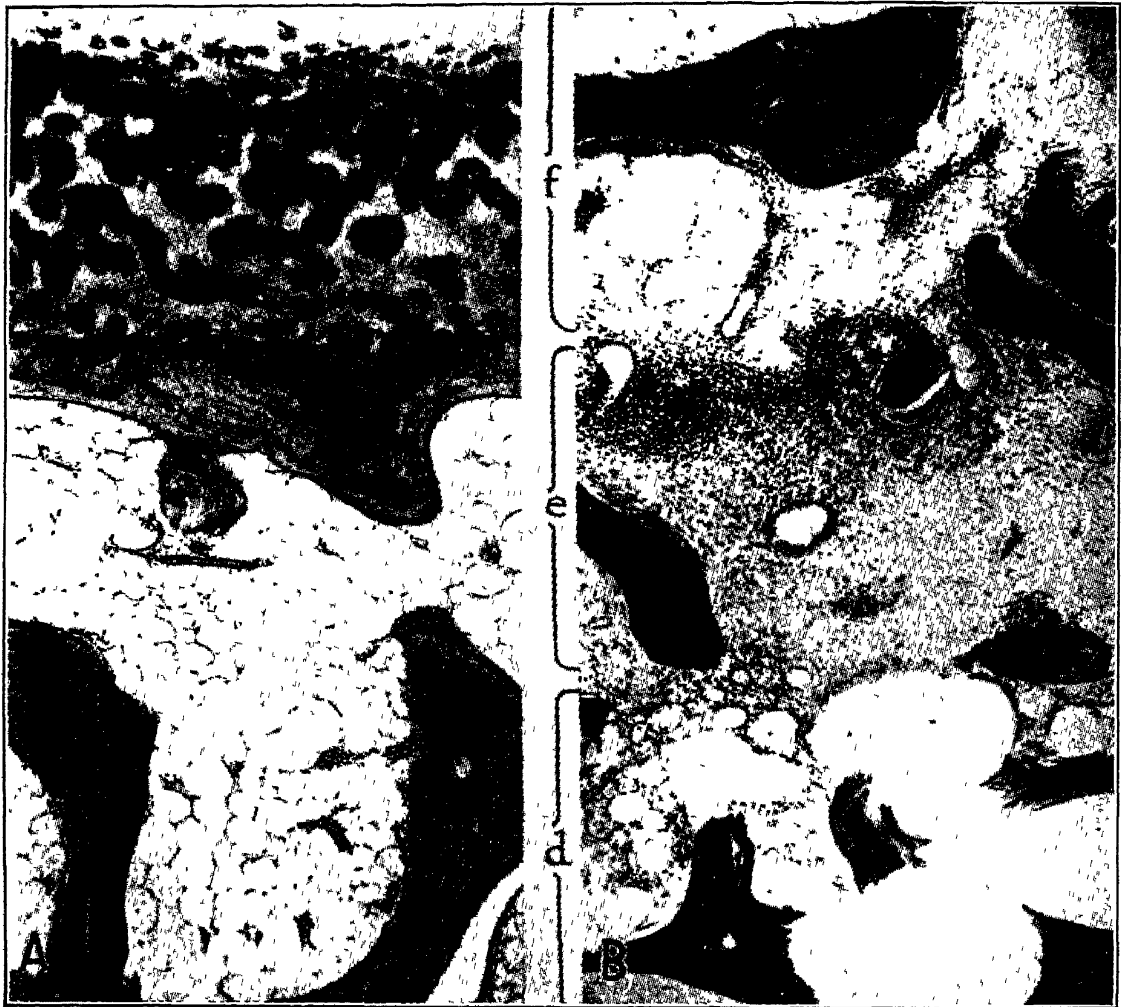


Fig. 23 (Case 3)—*A*, Middle of ankle-joint surface of body. Bone and marrow necrotic. Cartilage stains poorly and surface eroded. *B*, Section of invading zone at  $x$  in Fig. 22, showing (*d*) old dead bone, (*e*) zone of fibrous invasion, and (*f*) zone of replacement by new bone and marrow. (Phemister: Arch Surg.)

possible in the adult that there is a collapse of the head from weight bearing during the stage of creeping replacement by new bone.

#### Albers-Schönberg Disease

Van Creveld and Heybroek<sup>33</sup> reported the study of 2 cases of marble-bone dis-

been indicated in previous reports. The infant had 2 siblings in whom Albers-Köhler's disease was diagnosed. The other child had a normal mental development but was retarded in physical growth. The head was enlarged as a result of thickening of the cranial bones as well as a slight hydrocephalus. The



child had had repeated bone fractures after slight trauma. There was no general thickening of the cortical and spongy bone tissue but in typical places (skull, ribs, vertebrae and femurs) the osteosclerosis was so marked that there was no difference on close inspection between the cortex and the cancellous bone. Long bones had the characteristic clubbing. There were bands running parallel to the line of the epiphysis especially noticeable in the bones of the hands and feet. These were ring-shaped

end of the femurs, the peculiar shape of the head and more or less incomplete teeth. No therapy was suggested for the disease.

### **Congenital Bowing and Pseudarthrosis of Lower Leg, Manifestations of von Recklinghausen's Neurofibromatosis**

Five cases of pseudarthrosis cited by Barber<sup>34</sup> developed in children showing manifestations of von Recklinghausen's neurofibromatosis. Four were girls in

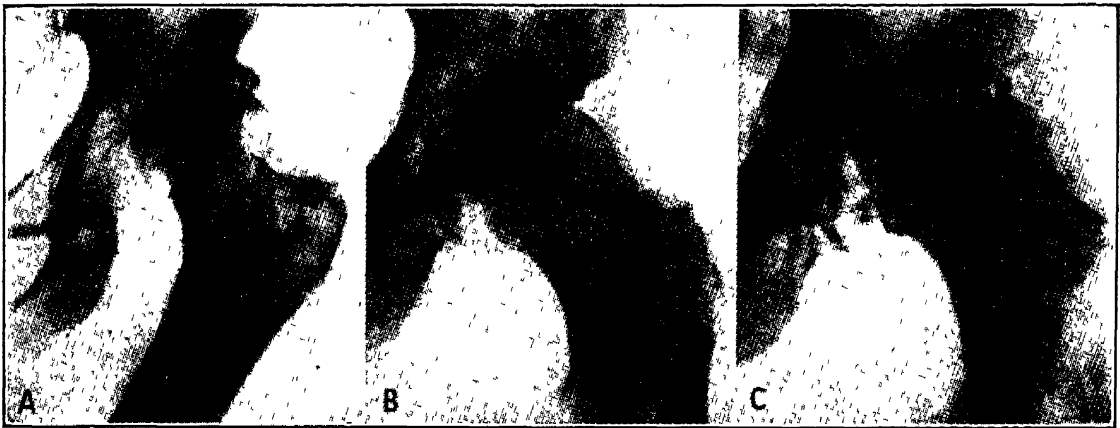


Fig. 24—*A*, Recent dislocation of hip, with chip off posterior acetabular margin; *B*, condition 81 days after reduction, *C*, condition 18 months later. (Phemister. Arch. Surg.)

in the scapula and ossa ilii. These were attributed to periodic fluctuations in the process of sclerosis. There were no symptoms indicative of endocrine disturbance in either child. Biochemical tests gave normal values for calcium, inorganic phosphorus, magnesium and phosphatase.

The authors believed the absence of anemia was an argument in favor of the bone anomalies of osteosclerosis fragilis generalisata as this was primary and not dependent on the damage to the bone-marrow.

Diagnostic of the disease was the atrophy of the optic nerve, the tendency to bone fractures, the malformation of the thorax, the thickening of the lower

which bowing was present in the lower legs at time of birth (Figs. 25 and 26). Pseudarthrosis followed fracture in 1 case, osteoclasia in another and osteotomy in a third. In the 1 boy, deformity prior to the fracture was not definite. In 1 family, the mother (Fig. 27) and 7 of 8 surviving children presented typical lesions of the disease. In another family, the father showed external lesions in addition to the associated scoliosis.

In substantiation of this observation, Barber reviewed Ducroquet's account in 1937 of 9 cases of congenital bowing presenting manifestations of von Recklinghausen's disease, 5 of whom had pseudarthrosis.

### Osteitis Deformans

Brunner<sup>35</sup> reviewed 26 cases of osteitis deformans (Paget's disease) which were observed during the past 10 years. In 70 per cent the diagnosis was arrived at by Roentgen examination rather than presenting symptoms or signs. Prodromal symptoms averaged 6 years be-



Fig. 25—Photograph of M. G., showing present lower leg deformity. (Barber: Surg., Gynec. and Obst.)

fore they were recognized by the physician. The earliest symptoms were noted between 31 and 65 years. The incidence in men and women was as 19 to 17. There was but 1 incidence of familial history. Seventy per cent complained of rheumatic symptoms, 20 per cent had pathological fractures and 10 per cent were symptom free.

Spontaneous fractures were rare in the absence of extensive osteoporosis.

The fractures involved, in order of frequency, were the tibia, femur, pelvis, humerus, vertebrae, skull, scapula, fibular, sternum, ribs, tarsals and phalanx. All traumatic fractures healed and deformity was infrequently the result. Deformity of bones was accredited to unilateral increase in growth and muscle pull.

The Roentgen pictures were characteristic; no cysts were observed. Joints were not involved. Nerve disturbances from bony encroachment of the skull were rarely observed. The blood phosphatase was increased in relation to the severity of the disease with a single exception. The blood calcium was not increased and in one-half of the cases was a low normal. A mild increase in blood phosphorus was frequently found. There was no abnormal loss of calcium or phosphorus in the urine or feces. The only endocrine disturbance observed was a fairly frequent increase in metabolic rate indicative of an increased thyroid function.

### Osteogenic Sarcoma

**Treatment**—The first 400 cases of undisputed osteogenic sarcoma recorded in the registry of Bone Sarcoma of the American College of Surgeons were reviewed by Ferguson.<sup>36</sup> He found the higher percentage of survivors occurred at the clinics having the higher percentage of late amputations. In the cases registered in later years, early amputation was more frequently used. This resulted in a decrease of survivors from 11.6 to 2.5 per cent. Females were treated without amputation more often than males who had early amputation. This did not cause the females to have the higher death rate. In 82 cases seen within 2 months of onset of symptoms and treated by amputation, the author

could find no explanation in age, site of tumor, variation in treatment or degree of malignancy estimated histologically as explaining the early deaths. No case

tion. The only subjects who did survive were those who had a lesion at the distal portion of the femur or the proximal portion of the tibia and were between



Fig. 26—Photograph of M. G., showing pigmented skin areas associated with von Recklinghausen's disease. (Barber: Surg., Gynec. and Obst.)

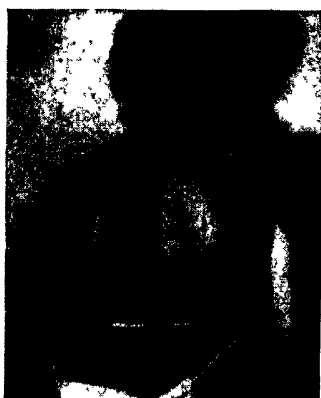


Fig. 27—Photographs of front and back of M. G.'s mother. Degree and extent of neurofibroma molluscum have not changed since M. G. was first seen in 1930. (Barber: Surg., Gynec. and Obst.)

which was treated by amputation in the first month after onset of symptoms survived. Subjects aged 1 to 10 or over 20 years failed to survive early amputa-

tion. The only subjects who did survive were those who had a lesion at the distal portion of the femur or the proximal portion of the tibia and were between the ages of 11 and 20 years. From the available statistics the author recommended for treatment while the amputation was delayed:

1. *Radiation*
2. *Excision and radiation*
3. *Excision and implantation of bone graft or chips, with or without radiation.*

If excision was used, Ferguson advises that it should be repeated if recurrence became evident before amputation was performed. The interval between the last excision and amputation should not be less than 3 weeks and probably should not exceed 2 months. The optimum time for amputation was a period when the patient was not losing weight, when the phosphatase content of the blood was not elevated, when there had been no sudden or marked increase in pain or swelling for 2 months and when there had been no increase of the mass or destruction demonstrable roentgenographically. Such periods occurred after the first 6 months of osteogenic sarcoma and were produced earlier in the course of the disease with the aid of radiation.

### Neurilemmoma of Bone

Attention is called by DeSanto and Burgess<sup>37</sup> to a tumor originating from the nerve sheath which was classified by Stout as a neurilemmoma. The tumor is encapsulated, the capsule consisting of the epineural sheath, and is attached to a nerve. The latter may be so small that it is not apparent to the surgeon. The shape of the tumor is fusiform, it is slow-growing, frequently soft and fluctuant, has a pink to gray appearance and is extremely vascular. It appears as a cystic expansive area in the midshaft of a long bone. Due to its origin from the nerve sheath in the bone cortex or in the periosteum, it may invade and excavate bone by direct extension, as occurred in 1 reported case, originating from the fifth lumbar nerve, invading the sacrum. Microscopically, 2 types have been described: Type A, the nuclei, which ap-

pear in a palisade formation about thin wire-like fibrils; type B, a loose reticular arrangement of cells and fibrils with microcystic spaces. This type is extremely vascular.

*Symptoms* are not marked. In the case of long bones, the first indication is a painless mass which is disclosed by

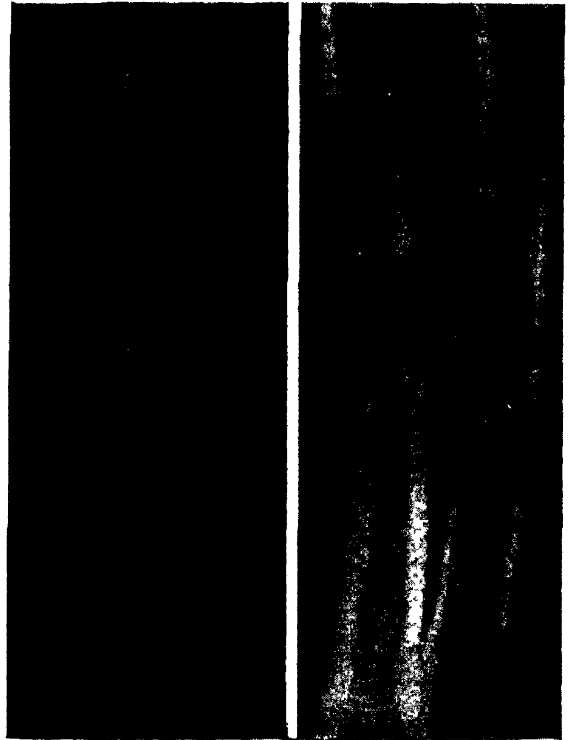


Fig. 28—A, Neurilemmoma midshaft of right ulna, Case 1, July 18, 1932. B, Roentgenogram taken May 21, 1935. (DeSanto and Burgess: Surg, Gynec. and Obst.)

x-rays as being a cystic lesion involving the medulla and cortex. In a case observed by the author, a pathological fracture was the first indication. Painful pressure symptoms may occur as a result of expansion of the tumor, as was the case of the tumor which originated in the sacrum. Both the author's cases were young adults. The tumor mass was evacuated in either case and was not followed by a recurrence (Fig. 28).

The *differentiation* of the tumor from the neurofibroma of bone or von Reck-

linghausen's disease was based on the absence of other skeletal changes, such as scoliosis, lordosis, unilateral hypertrophy of the extremity, localized cortical and subperiosteal reaction and the pseudarthrosis. The pathological section was another aid in differentiation. Neurogenic sarcoma was distinguished by

great majority of the cases of low-back pain are due to minor injuries to the soft tissues. These injuries are not unlike the strain and tears of the tendinous and periosteal attachments of muscles which occur in other parts of the body and manifest themselves by identical signs, *i e.*, the distinct and sharply

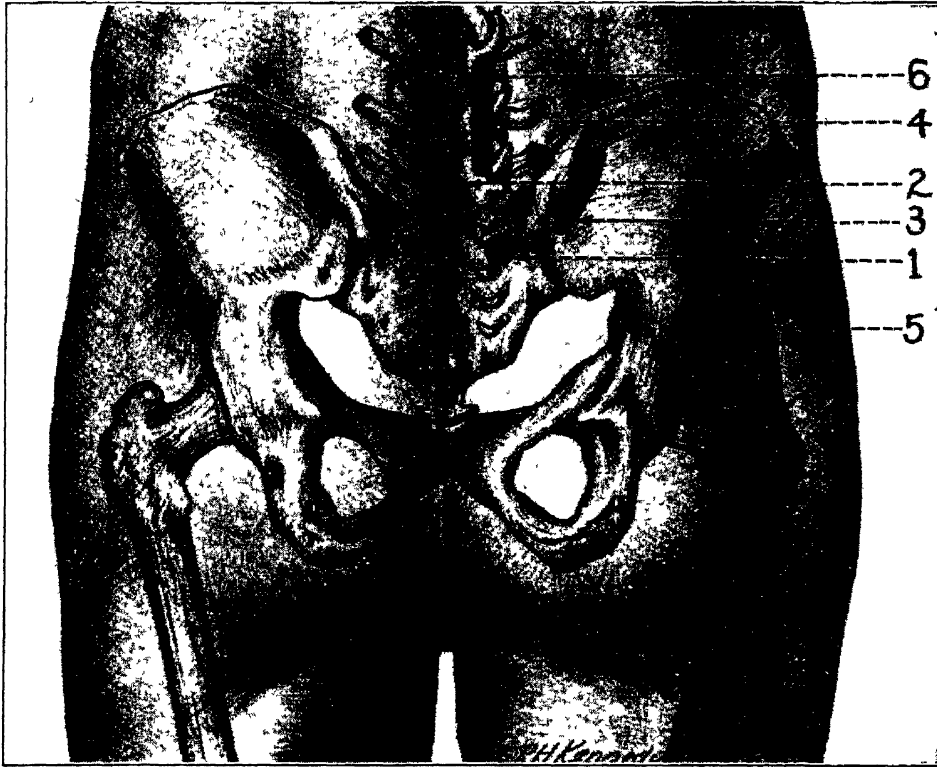


Fig 29—Grouping of "trigger points"

- |                            |                                  |
|----------------------------|----------------------------------|
| 1. Sacrospinalis syndrome. | 4. Transversosacral syndrome.    |
| 2. Lumbosacral syndrome.   | 5. Tensor fasciae latae syndrome |
| 3. Gluteal syndrome        | 6. Myofascial syndrome           |

(Steindler: J. Bone and Joint Surg)

shorter duration of symptoms, severe pain and the absence of clear-cut defect in bone by x-rays. It was not as easily differentiated from chondroma except that the defects were more apt to be in the shaft. Differentiation of osteitis fibrosa cystica was made by the lack of other cysts and normal blood chemistry.

### Syndrome of Low-Back Pain

**Interpretation of Sciatic Radiation** — According to Steindler,<sup>38</sup> the

defined pressure point, a certain attitude of relief assumed voluntarily to prevent further strain, and a tendency for the involved structures to respond favorably to immobilization.

In cases of low-back pain, there is a stereotype pattern of pressure or "trigger points" (Fig. 29). Sciatic radiation is of purely reflex origin and the clinician should divorce himself from the idea that there is direct mechanical irritation of the sciatic nerve or its component roots

in connection with low-back pain. A substantiation of this is the fact that the reflex phenomenon follows and does not precede the low-back pain. The afferent branch of the reflex arc is furnished by the sensory fibers supplying the injured muscular, ligamentous and aponeurotic structures and that the connection with the sciatic nerve is made through the spinal ganglia or possibly in the spinal cord. If the so-called "trigger point" irritation is exaggerated, the sciatic pain is increased. On the other hand, upon injection at this point with novocain, local pain as well as sciatic radiation disappeared and the leg signs at once became negative.

There are 3 possible, exceptional groups of *sciatic radiation*. The *first* is when the lesion is in the spinal canal, as with a tumor, herniated disc or hypertrophied ligamentum flavum. A diagnosis of this lesion is based on the high incidence of clinical neurological signs, the primary appearance of sciatic radiation, the high spinal-fluid protein and the demonstration of a spinal block. The *second* is sciatic radiation as the effect of radicular compression. This is much less well founded. Congenital anomalies, such as tropism, laxity of the neural arch, spondylolisthesis and sacralization, the author believes are only indirectly responsible for sciatic radiation, in that they facilitate and favor ligamentous and muscle strain. The *third* group are those with arthritic proliferations about the intervertebral foramina which may be responsible for direct compression of the sciatic roots. The author questions the compression theory with the fact that paresthesia and signs of spinal irritation are not complained of except in the purely arthritic type who have paresthesia and sensation of chills and heat with or without the sciatic radiation.

The "trigger-points" are grouped as follows:

1. *Sacrospinalis Syndrome* (Fig. 29, No. 1)—There is a pressure point at the posterior superior or inferior iliac spine. This was treated by **support**.

2. *Lumbosacral Syndrome* (Fig. 29, No. 2)—Pressure point is at the lumbosacral junction. This was treated by **support**, **lumbosacral fusion** and where there was found an impingement of the lumbar spinous processes, **resection of the spinous processes** was sufficient.

3. *Gluteal Syndrome* (Fig. 29, No. 3)—Pressure point is at the gluteus maximus insertion. This generally responded to conservative **immobilization**. At times it was necessary to **strip the myofascial attachment of the gluteus maximus from the posterior superior spinous process of the ilium**.

4. *Transversosacral Syndrome* (Fig. 29, No. 4)—Pressure point was at the transversosacral articulation in cases of sacralization of the fifth lumbar vertebra. If **immobilization** failed, **resection of the articulation** was often necessary. At times a **fusion of the transverse process articulation** was done with relief.

5. *Tensor Fasciae Latae Syndrome* (Fig. 29, No. 5)—There was a tender point at the lateral border of the fascia and iliotibial band with a positive Ober sign. In many cases there was a positive Ober sign but it was only significant if associated with tenderness of the iliotibial band. A **division of the aponeurotic structure** which covers the gluteus medius and blends with the iliotibial band, in combination with **rest** and **exercise**, or any of these measures alone, accomplished results.

6. *Myofascial Syndrome* (Fig. 29, No. 6)—There is a vague tenderness along the sacrospinalis muscle and its fascial sheath. The treatment of this was by **immobilization** and local measures such as **heat** and **massage**.

### Spondylolisthesis

Interesting observations were made by Hitchcock<sup>39</sup> in 3 cases of spondylolisthesis, in which there was a gradual progression of the deformity over a period of years (Figs. 30 and 31). He was unable to substantiate trauma as being a factor in the increased deformity. In

reviewing a series of fetal spines, he concluded that the defect was not due to lack of ossification of the accessory processes. In experimenting with stillborn babies and infant cadavera, he found that forced flexion would produce a

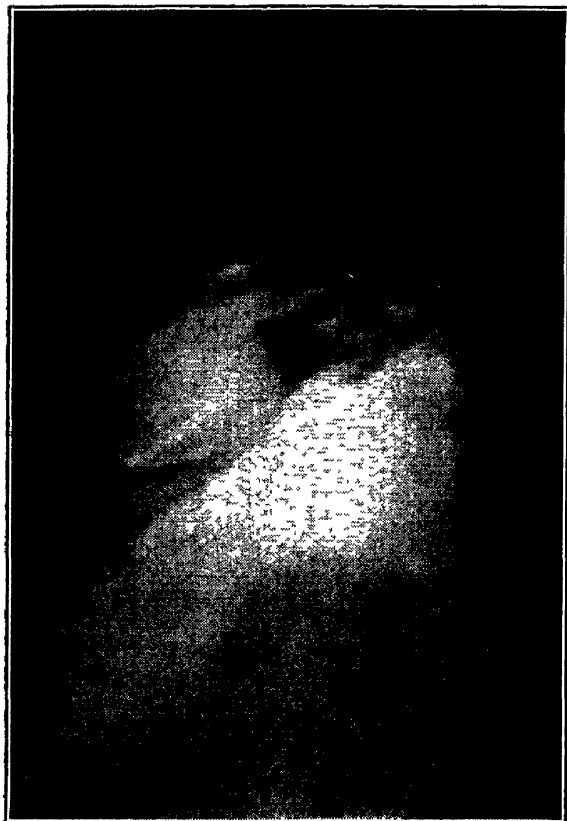


Fig. 30—Mrs. D. C. W., aged 42 years. Lateral view of lumbosacral region taken in 1932, showing slight spondylolisthesis with fifth disc intact. (Hitchcock: J. Bone and Joint Surg.)

fracture of the accessory processes which was frequently unilateral and in the majority of cases bilateral. The unilateral fractures were produced by combining flexion with lateral bending or torsion. No fractures were produced by hyperextension. He concluded that such a fracture of the neural arch occurring in early infancy would account for a union by fibrous tissue or cartilage and the subsequent development of a pseudarthrosis which was found in conjunction with spondylolisthesis.

### Spondylitis Infectiosa

Spondylitis infectiosa, according to Bade,<sup>40</sup> occurs after infectious diseases such as scarlet fever, smallpox, influenza, malaria and typhus. It appeared following generalized bacterial infections with pneumococci, staphylococci, streptococci and brucellosis. Based upon the clinical observations of 10 cases, he regarded the x-ray findings characteristic: A narrowing of the involved intervertebral disc—this narrowing was frequently only confined to a sector of the disc; small irregularities and defects in the adjoining portions of diseased vertebra which

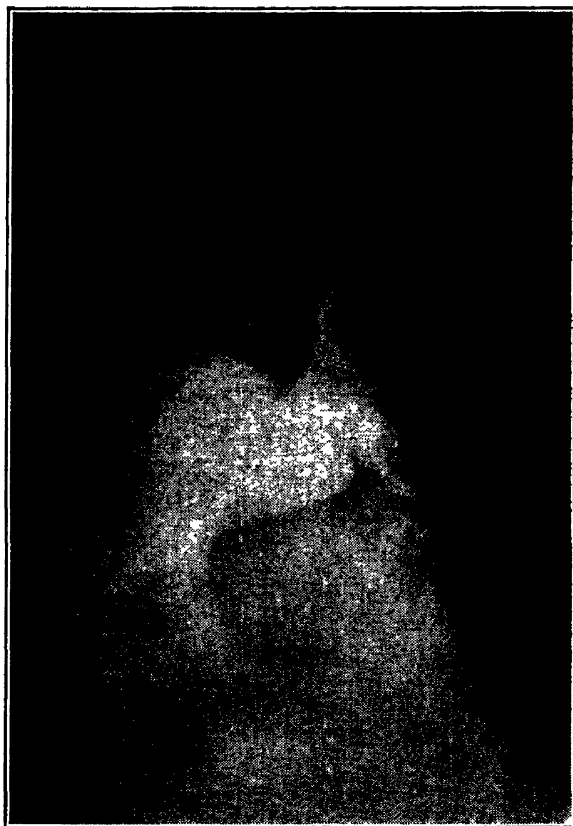


Fig. 31—Mrs. D. C. W., aged 45 years. Film taken in 1935 shows further slipping and disappearance of disc between fifth lumbar vertebra and sacrum. (Hitchcock: J. Bone and Joint Surg.)

were of a greater density; and the rapid appearance of reactive proliferations of bone which developed into bridging bands.

The *differential diagnosis* of spondylitis infectiosa from osteomyelitis of the spine was based on the more rapid course in the acute cases of osteomyelitis which frequently terminated fatally and in the subacute and chronic cases of osteomyelitis on the Roentgen film, which showed scoliosis of the vertebra and areas of fused bone tissue. The clinical course was of additional value in differentiation.

Tuberculosis and osteochondrosis of the intervertebral discs were dependent upon the Roentgen film. In the latter especially, the narrowing of the disc was uniform; there were no defects in the terminal plates but a loosening of the structures of the disc with subluxation of adjoining vertebral bodies.

#### **Influence of Fusion of Spine on Growth of Vertebrae**

In an effort to determine the effect of fusion of the vertebrae on the growth of the spine, Haas<sup>41</sup> performed a series of experiments on growing dogs in which the vertebrae were fused by either the Hibbs or the Albee method. Wire markers were used in the extremes of the operative area and, again, by means of an abdominal approach placed in the bodies of the vertebrae. Treating dogs of 2 months of age for the operative work, there was approximately 210 days left for growth. In the *Hibbs type* operation, it was found that the body increased in size and the markers separated. There was apparent lengthening between the markers, as the callus caused by the fusion was still soft. As soon as the fusion became firm, there was no further yielding in the fused spine. This was evidenced by compression of the disc, the bulging anteriorly of the bodies and a premature ossification of the epiphyseal plates, particularly in the posterior portion. With the *Albee*

*type* of fusion there was much less separation of the markers in the spinous processes, due to an earlier fixation of the spines of the vertebrae. The general effect of both types of operations was to cause a lordotic deformity of the spine.

#### **Scoliosis Following Empyema**

Selig and Arnheim<sup>42</sup> state that scoliosis resulting from empyema is of 2 types: (1) In scoliosis following empyema, the concavity of the curve is toward the side of infection, and there is no rotation of the vertebral bodies; (2) in scoliosis resulting from thoracoplasty, the convexity is toward the side of the resected ribs. Sixty-five cases of empyema which had operative drainage at the Mt. Sinai Hospital, New York, from the years 1932 to 1936 were surveyed. Fifty-two patients with acute empyema whose wounds healed within 4 months had no persistent scoliosis. Of 13 patients with chronic empyema requiring multiple operations, 5 developed a persistent scoliosis. These were under 13 years of age. Two were very marked—1 had a 97° curve. He had a thoracoplasty at the age of 12 years. The convexity was on the side of the operation, with considerable rotation of the vertebral bodies. Conservative treatment with jackets and braces had been of no value in preventing or correcting the curve. The other case had chronic empyema on which numerous operations had been performed since 2 years of age. The concavity was toward the diseased side without rotation but had progressed in spite of care.

#### **Benign Chondromas of Ribs**

In a review of the 9 chondromas of ribs which were proved by biopsy and excision, appearing in the literature, and 2 additional cases, Harper<sup>43</sup> realized



that the most probable theory concerning the etiology was that the tumors arise from cartilaginous fetal rests or islands of cartilage resulting from old rickets. The tumor generally developed slowly. Occasionally a traumatic incident could be recalled. The pathologic picture was that of transition between osteochondroma and malignant chondromyxosarcoma. Cartilage predominated the picture but changes might occur during development, so that the chondroma might become osseous or undergo malignant degeneration to become a chondromyxosarcoma. Chondromas in the ribs were regarded as potentially malignant even though they appeared histologically benign, as there was such a strong tendency for a chondroma in this region to undergo malignant degeneration. Clinically, this change was indicated by sudden increase in size of the tumor or an increase in the pain. It was learned that benign chondromas were very prone to recur and incomplete removal stimulated the growth of the remaining tissues. Of 11 cases followed more than 1 year, 5 had recurrences. The treatment recommended was *early and complete removal of the tumor*. It was believed necessary to open or resect part of the pleura for complete removal. Other authors advised *radium* or *Roentgen therapy after the surgical removal*.

### Osteomyelitis

**Treatment**—In discussing the treatment of pyogenic osteomyelitis, Phemister<sup>44</sup> emphasized the importance of conservatism. Ninety per cent of osteomyelitis was due to the staphylococcus. The portal of entry could not be detected in 75 per cent. The microorganisms were fed into the blood stream from some small hidden focus of infection. These microorganisms lodged in the sinusoidal spaces of the circulatory sys-

tem or clumped together and blocked the smaller blood-vessels as emboli. Large septic emboli creating massive infarction was rare in osteomyelitis.

The evolution of the osteomyelitis varied after development. The severe type spread rapidly and destroyed bone. The localized type gave slight local and moderate general symptoms. The treatment of the *severe type*, contrary to past teaching, did not call for immediate surgery. In infants, the lesion localized at the bone end. The bone cortex was thin and the abscess formed in the peripheral tissues early. The treatment was concerned with the general infection and incision of local abscess. The general infection, the septicemia and the toxicity were combated with *intravenous fluids*, *blood transfusions* and *chemotherapy (sulfapyridine and sulfathiazole)*. The involved extremity was *immobilized*. When *abscesses* localized in 3 to 7 days and appeared external to bone, they were *drained* by simple incision facilitated by *local anesthesia*. *Aspiration* was of aid in detecting the site of the abscess to be drained. If the subject remained ill and no abscess formed after a few days, the cortex of the bone was opened.

The *subacute* and *chronic stages* of osteomyelitis demanded the earliest possible *operative care*. This necessitated the removal of dead bone and the effacement of cavities. As much chronically-infected bone was removed as was compatible with the continuity of the shaft. Subperiosteal resection was rarely indicated, except in ribs and fibula. The mode of dressing was of minor importance as long as absolute *immobilization* of the extremity was observed. The packing was removed in 3 to 6 days. Afterward, superficial dressings were done as indicated. The author attributed

no particular merit to vaccines, serums, maggots or bacteriophage.

### Acute Hematogenous Osteomyelitis

**Treatment by Asparagin Bacteriophage**—MacNeal<sup>45</sup> draws comparisons between 36 cases of *Staphylococcus aureus* septicemia with osteomyelitis who did not receive bacteriophage and 12 cases with positive blood cultures for *Staphylococcus aureus* with osteomyelitis who did receive bacteriophage. Of the former group there was a mortality rate of 80.5 per cent. This mortality rate was practically identical for those of other reported series receiving no treatment other than surgical drainage, those who received antitoxin, those who received sulfanilamide, those who received several blood transfusions and 9 who received minute doses of broth bacteriophage.

Of the second group, but 1 case died. This was a mortality rate of 8.3 per cent. All patients in this group received stock bacteriophage for the first few days during the interval in which the specific type was being prepared. The initial dose was 5 cc. intravenously followed at 45-minute intervals by 10, 20, 30, 40 and 50 cc. doses. The dosage was discontinued when the subject had a shock reaction or had received a total dose of 500 cc. The symptoms of shock were complaints of cold, pallor, cyanosis and chattering of teeth. In addition to the bacteriophage, surgical measures, blood transfusions, sulfapyridine, neoprontosil and antitoxin were given. The ages of the patients varied from 3 to 20 years. They were classified into 3 groups, *i. e.*, (1) the patients who had more than 1 positive blood culture, who were critically ill and developed metastatic foci—there were 7 in this group with 1 death; (2) patients who were critically ill, with more than 1 positive blood culture and

no metastatic foci—in this group there were 2 patients and no deaths; (3) patients who had 1 or more positive blood cultures, who were not severely ill and did not develop metastatic foci—in this group there were 3 patients with no deaths.

The author concluded that a larger dosage of bacteriophage used in connection with the other treatment certainly influenced the course of the disease in these patients.

No mention was made of any instances in which shock failed to be reduced; in an earlier article by MacNeal and Frisbee, it was stated that a second and third attempt to shock the patient was made on the fourth and again on the seventh day if the blood culture remained positive. These writers further mentioned the continuation of small intravenous doses twice daily for 1 to 2 weeks and then gradually tapering off to 2 to 3 doses for 6 months.

### Staphylococcal Infection— Correlation Between Clinical and Experimental Findings

Working with 35 cases of *Staphylococcus aureus* isolated in the blood stream in cases of staphylococcal infection, Kleiger and Blair<sup>46</sup> attempted to correlate the relationship of the formation of a staphylococcal toxin to the fatality of a staphylococcal infection. They cited the clinical illustration of a potent staphylococcal toxin with 21 children in Bundaberg, Australia, who received a prophylactic injection of diphtheria toxin-antitoxin which had been contaminated by a highly toxigenic strain of staphylococcus. Twelve of the 21 children died in 36 hours. Their initial symptoms were cramps, vomiting, diarrhea, cyanosis, rapid pulse, temperature rise and, finally, convulsions. Experimentally, it was found the staphylococcal

cultures with saline suspensions injected intravenously into rabbits react in 3 ways: One-third of the cultures studied produced sufficient toxin *in vivo* to kill the rabbits within 10 to 18 hours. A few strains produced toxin more slowly and killed the rabbits in 20 to 36 hours. In the first group, the death of the rabbits was typical of a highly potent toxin reaction. In the second group there was a tendency toward localization in development of areas of infarction in the cortex of the kidneys. In the third group, which were one-half, the animals survived from 2 to 12 days after inoculation. There were no signs of early toxin formation. At autopsy they either had multiple abscesses of the kidneys or myocardium.

An attempt was made to use antitoxin in conjunction with the intravenous dose of staphylococcal culture. Rabbits receiving the highly toxigenic strain of staphylococcus survived  $2\frac{1}{2}$  to 5 times as long as the unprotected controls. They eventually died with multiple abscess formation rather than toxicity alone. When nontoxigenic strains of staphylococcus were used, the animals receiving the antitoxin did not survive any longer than the controls.

In reviewing 35 cases of staphylococcal infection with positive blood cultures, it was found there was a mortality rate of 66 per cent. It was noted that the infections which invaded bones and joints were less lethal than those of the soft tissues. The cases could be divided into 2 groups on the basis of certain consistent clinical characteristics. Fourteen exhibited clinical symptoms which could be attributed to the effects of the toxin. All were under 30 years of age. Eleven died. The onset of the infection was generalized, as described for the acute toxic infection. This included acute gastrointestinal disturbance, such as ano-

rexia, nausea and vomiting, associated with indefinitely localized abdominal pain. There was diarrhea with watery, foul-smelling stools and later incontinence. Early irritability and restlessness were followed by coma and delirium before death. Rigidity of the neck was present in most of the cases. Lumbar puncture was normal. The subjects were generally wet with perspiration, had cyanosis of the lips and fingernail beds. The temperature was elevated and pulse rate elevated. None of the patients had chills. Frequently they had embolic phenomena in the skin and conjunctivae. Urine examination revealed changes characteristic of renal irritation. Changes in the white blood-cells were not significant to permit differentiation from the nontoxic group. Post-mortem examination of the patients revealed few, if any, metastatic areas of infection. These, when present, were very small and early, being in the nature of infected infarcts rather than true abscesses. There were hemorrhagic lesions of the myocardium, skin and gastrointestinal mucosa and renal cortex.

Fifteen patients showed none of the symptoms attributable to the effects of the toxin. All these were over 30 years of age. The 6 remaining cases were classified in the miscellaneous group, as the blood stream infection was a terminal invasion as a result of infection in some vital organ. One had a brain abscess, another had meningitis and another had phlebitis of the portal vein. These cases were all adults. The other 3 had a recurrence of osteomyelitis with invasion of the blood stream.

### **Epiphyseal Changes in Acute Infections of Bone**

Of 2064 patients with acute and chronic osteomyelitis encountered in the Mayo Clinic, Macey<sup>47</sup> found 66 who showed definite clinical and roentgeno-

logical evidence of epiphyseal involvement. This did not include the cases in which there was closure of the epiphyseal line as a result of a low grade infection without the acute symptoms of hematogenous osteomyelitis or those resulting from acute traumatic osteomyelitis. Other cases were the subjects who had lengthening of the extremities without demonstrable changes in the epiphyseal line or where a pathological lesion was too far distant from the

defects were observed in this entire group (Fig. 33), varying from genu valgus, ankylosis to shortening. Eight cases had involvement of the distal tibial epiphysis. Two occurred in infancy, the remainder around 14 years of age. All presented deformity. The proximal tibial epiphysis was involved in 6 cases. Two showed no deformity but 1 of these had a lengthening of the leg. Proximal humeral epiphysis involved 4 cases; all showed deformity. The lower fibular

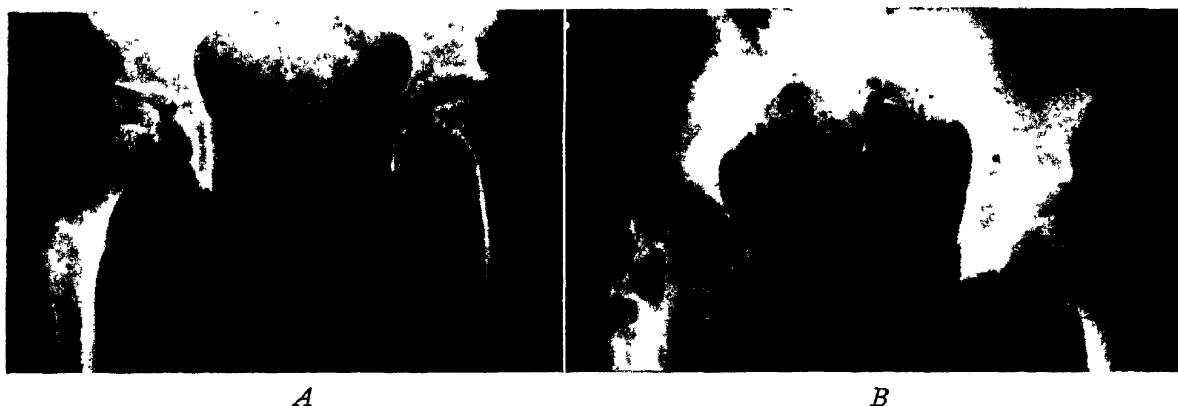


Fig. 32—*A*, Characteristic changes in hips after early incision and drainage. Absorption of epiphysis and portion of neck of femur. *B*, Preservation of epiphysis and bony ankylosis. (Macey *Am. J. Surg.*)

epiphyseal line to be considered a source of irritation. In the upper femoral epiphysis there were 27 cases and in no instance had the epiphyseal line been spared (Fig. 32). In but 2 cases did the epiphysis remain; in 1 the head of the femur was markedly distorted, in the second the head of the femur was smaller than that on the opposite side and there were absorptive changes and irregularity of the ilium. In this group of 27 cases, the age of onset ranged from 7 to 19 years, with the exception of 1 infant. The general outcome was absorption of the epiphysis and varying degrees of absorption of the neck of the femur or ankylosis of the hip-joint.

Involvement of the lower femoral epiphysis occurred in 15 cases. Residual

epiphysis was involved in 2 cases and these showed no residual defect. The acetabular epiphysis was involved in 2 cases, ages 11 and 12 years; both showed closure of the epiphysis of the acetabulum and deformity.

In conclusion, it appears that the occurrence of epiphyseal changes associated with infections of long bones is common in those cases in which there is surgical trauma to the epiphysis. Where the epiphysis is within the joint, however, such as the proximal femoral epiphysis, distal femoral epiphysis, the changes occur without relationship to the treatment. It was ventured that trauma to the epiphyseal disc before the infection occurred might account for other epiphyseal changes. Another pos-

sible thought to explain the changes was the irritation of a sequestrum lying adjacent to the epiphyseal line. In those cases in which the adjacent epiphysis appeared to have healed without residual deformity, on subsequent roentgenological examination, the destruction appeared to be explained by the possibility of blood-borne infection being deposited in the epiphysis with resulting degeneration. Involvement of the epiphyseal line could result in 2 ways, *i. e.*, (1) from

clinical end-results appeared to be the hips ankylosed in good position. In the case of tibial epiphysis, "surgical insult at the time of surgical drainage" appeared to account for the changes. Finally, it was cautioned that the surgeon should guard against mistaking acute synovitis of the joint for suppurative arthritis in the course of an acute metaphysitis, as drainage of such a joint would cause suppurative arthritis and residual epiphyseal changes.



Fig 33—*a*, Involvement of lower femoral epiphysis 18 days following incision and drainage; spotted absorption of medial epiphyseal line, *b*, 4 months following onset, beginning recalcification of affected portion, with large region of absorption in medial portion of epiphysis; *c*, 10 months following onset; closure of medial femoral epiphyseal line, especially along periphery; early genu valgum. (Macey. Am J Surg)

absorption and (2) from deposition of calcium in the cartilaginous disc. An interesting observation was the fact that 2 cases which showed roentgenological evidence of epiphyseal involvement but had no pressure on the epiphysis during the time of infection, a pathologically dislocated hip and a distal femoral epiphysis treated with traction, had no subsequent degeneration of the epiphysis. It was suggested that pressure might play some part in the amount of destruction and absorption of the epiphysis. It was concluded that in proximal femoral lesions the best treatment was **early immobilization and traction** rather than early incision and drainage. The best

### Osteochondritis Dissecans of Hip

Two cases of osteochondritis dissecans of the hip-joint are reported by King and Richards<sup>48</sup> (Fig. 34). Symptoms of this condition were usually gradual in onset. They occurred in the third or fourth decade. Pain varied in its intensity in the same individual. It was generally accentuated by a prolonged period of use or strain on the hip-joint. This was followed by periods of remission. There was some limitation of hip motion, depending upon the amount of muscle spasm. There were never any instances of the hip-joint becoming locked. The pain often was referred to the knee, inguinal or gluteal region. The x-ray pic-

ture was characteristic and never failed to determine the diagnosis. Etiology of the condition was just as obscure as it was for other joints, such as knee and elbow, more commonly observed.

*Treatment* was **surgical** as the operative results for osteochondritis dissecans in knee- and elbow-joints were good in

ing occurred. The hip-joint was reduced and wound closed in layers. A **walking hip spica** was applied. The patient was allowed up on the tenth day. At the end of 3 weeks, the cast was removed. At the end of a month, crutches were discarded. These cases had been followed but 2 months. Their range of motion was

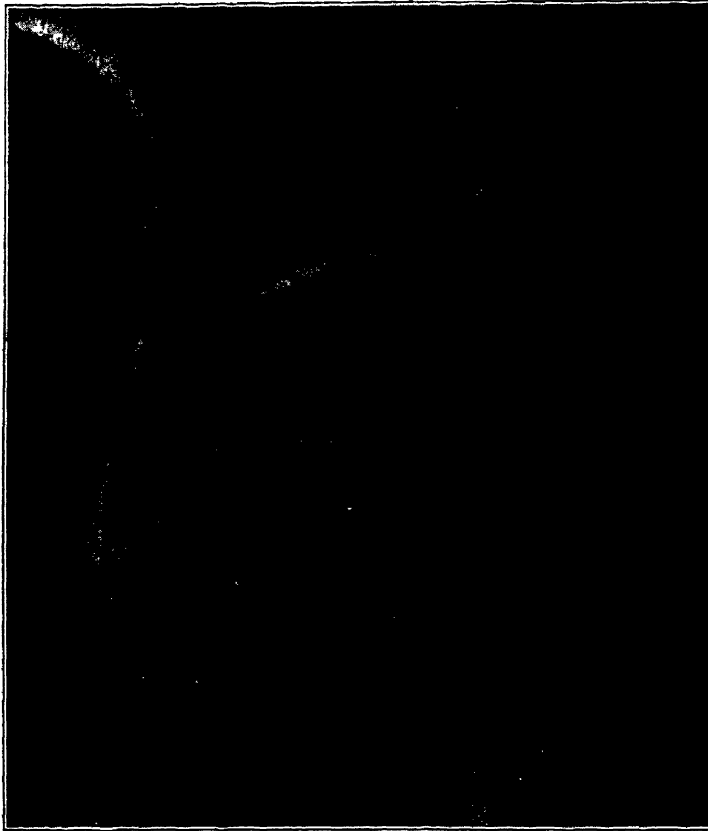


Fig. 34—Case 1. Before operation.  
(King and Richards: J Bone and Joint Surg)

90 per cent of the cases. The authors used the Smith-Petersen approach and dislocated the hip-joint (Figs. 35A and 35B). Desiccated areas of cartilage were identified and dissected free by using its line of demarcation from the groove in the cartilage and underlying bone. No bleeding was encountered in removing this segment. There appeared to be an underlying sheath of avascular tissue. The center of this was incised down to the underlying healthy bone and bleed-

equal to that of the opposite hip and they were free from symptoms.

### **Tuberculosis of Greater Trochanter and Trochanteric Bursae**

In 1017 cases of bone and joint tuberculosis, Wassersug<sup>49</sup> found 18 cases of involvement of the trochanter of the femur. Thirteen were males and 5 females. A history of local trauma was obtained in 9 cases. Diagnosis was based upon pain in the hip region, the appear-

ance of a lump and the development of a sinus. Pain was usually intermittent and accentuated by exercise or a change of posture. There were very few signs other than the swelling over the great trochanter and local tenderness. The motions of the hip usually were not re-

sinus. Six cases had been followed for a period of 4 years without evidence of recurrence. Incision and drainage proved of no value in any case. One subject had a resulting draining sinus for more than 25 years. Of the 18 patients, 4 are still hospitalized. Fourteen subjects re-



Fig. 35—A, Femoral head has been luxated from acetabulum. Clamp is on ligamentum teres. On superolateral aspect of femoral head the osteochondritic focus is readily visible. Note furrowing and imbrication of surrounding cartilage (King and Richards. J. Bone and Joint Surg.)

stricted. The roentgenogram revealed bone destruction in every case in this series. Differentiation from a neoplasm would be difficult from the roentgenograms. Histological or bacteriological, or both, methods were necessary to confirm the diagnosis.

*Treatment was radical excision, resection or thorough curettage.* These were performed in 10 cases and all were discharged from the hospital without a

remained at a sanatorium a total of 21¼ years. The shortest stay was 6 months, the longest 6 years. Prognosis of cases who had resection of the tronchanter with an absence of other tuberculous foci was excellent.

#### Tuberculosis of Large Long Bones of Extremities

In reviewing the English literature, Carrell and Childress<sup>50</sup> found that there

were about 32 reported cases of tuberculosis of the long bones. After circularizing the orthopedic surgeons of the United States and Canada, the authors were able to find 78 unreported cases. All cases in this series had been proved by microscopic section and animal inoc-

per cent had associated pulmonary infection. Only 12 per cent of the cases of long bone involvement had associated joint involvement. Of the cases with associated lesions, 50 per cent failed to survive. Sites of associated lesions other than the chest and joints were the me-



Fig. 35—*B*, Osteochondritic focus reflected upward by incising along cartilaginous grooving except superiorly. Clamp remains on ligamentum teres; forceps hold osteochondritic fragment (King and Richards. *J. Bone and Joint Surg*)

ulation. The tibia was involved in 29 per cent of the cases, the femur in 27 per cent. At time of onset, 48 per cent of the patients were 20 years of age or more, the youngest patient being 6 months, the oldest 75 years. In 48 per cent, the patients had complaints for less than 6 months; 43 per cent had symptoms for over a year. In 43 per cent of the cases, associated active tuberculous lesions were present. Approximately 30

ninges, skin, flat bones, middle ear and small intestine (Fig. 36).

**Treatment**—Of 13 patients who received no treatment, 8 died and 5 had spontaneous healing. A number of these subjects were moribund on admission and others had extensive involvement of bone and other tissues which made them a poor operative risk. The authors do not believe that shaft tuberculosis will heal spontaneously, as 43 per cent of



the patients had symptoms for over a year before operative intervention. *Amputation* and *excision* produced good results in 50 per cent of the cases. Of 44 per cent treated by incision and drainage, healing took place in 66 per cent. Many of these cases had draining sinuses

### Tuberculosis of Knee-Joint in Adults

Key<sup>51</sup> was able to review 99 adults treated for tuberculosis of the knee-joint from 1931 to 1935. A history of trauma bearing some relation to development of disability in the knee was obtained in 15 per cent. There was an average interval,

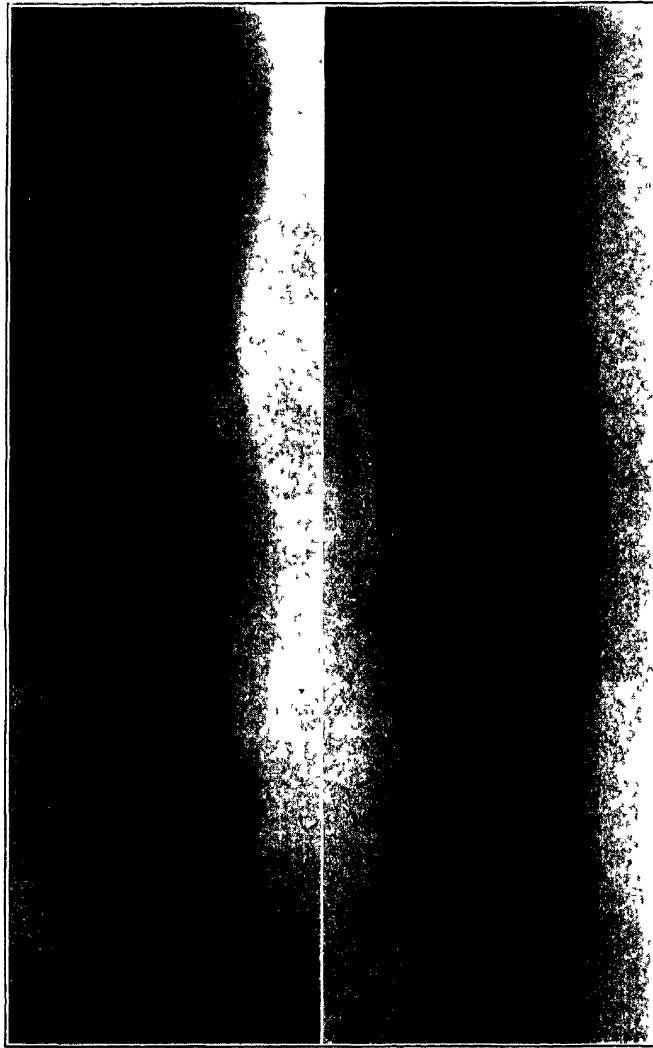


Fig. 36—Microscopic diagnosis Tuberculosis of left tibia. (Carrell and Childress: J Bone and Joint Surg)

which were not suitable for closure and others were treated under the mistaken diagnosis of pyogenic osteomyelitis. The 13 patients treated by *curettage* or *saucerization and closure* presented the best results with healing in 92 per cent.

however, before onset of symptoms, of 4½ months. Pain was the first symptom in 70 per cent. Swelling was the initial abnormality in 22 per cent. Tenderness, when elicited, was present on the mesial aspect of the joint. Local warmth was always present. Limitation of motion

was present when joint surfaces were eroded and was accompanied by muscle spasm. Abscesses in the early stage of the disease occurred in 65 per cent. In 87 per cent the diagnosis was made only after the pathological changes in the joint had passed the earlier stages of the disease. In 37 per cent tuberculous lesions were present elsewhere. The focal disease, the author believes, undergoes 3 changes:

1. Remains comparatively localized in the bone and reaches quiescence.
- 2 Extends laterally beyond the periosteal structures and causes abscess formation in the soft tissues.
3. Extends longitudinally, causing destructive changes in the joint with abscess.

The Roentgen film revealed early changes as follows:

1. General haziness.
2. Increased width of soft tissue shadow
3. Osteoporosis.
4. Diminution of joint space.
5. Thinning of cortical bone.

After 4 months, abscess cavities were found in the bone. The general physical condition of the patient was good in 87 per cent. Bacteriologic examination of aspirated pus was the greatest diagnostic aid. The *differential diagnoses* must be made between infective or gonorrheal arthritis, syphilis, hemophilia, traumatic arthritis or neoplasm.

*Treatment* in the synovial type, or when the bone foci were remote from the articular margin and surrounded by healthy bone, was *conservative*. This treatment sufficed in 33 per cent. *Surgical arthrodesis* after arrest of the general illness and local disease was regarded as the best treatment. This was done in 60 per cent. Of these, 83 per cent obtained bony union and excellent functional result. *Amputations* were done in 10 per cent with a 30 per cent mortality. Since amputation was a

last resort, it was delayed too long; the patient was then suffering from profound toxemia and could not be saved by removing a single focus of infection.

### Tuberculosis of Knee in Children

**Growth Following Fusion Operation**—Haas<sup>52</sup> reviewed 12 cases of tuberculosis of the knee-joint of children, the ages varying from 2¾ years to 12½ years. In all of the cases, a positive tuberculin test was elicited. The microscopic examination of the material removed from the knee-joint at the time of operation was positive for tuberculosis. In every case a *fusion operation* was done on the knee-joint. In the cases in which a flexion deformity existed, this was corrected by wedged plaster before operation. The cartilage of both tibia and femur were removed. Particular care was taken to keep away from the epiphyseal cartilage. The patella was left intact. A second operation was frequently required in 2 years' time to obtain firm bony ankylosis. The majority of the subjects showed no loss of growth and when it did occur, it was not more than ½ inch. In some subjects there was actual lengthening after operation, due to stimulation of the epiphysis. The knee was protected by a *brace* for several years following operation to prevent a redevelopment of a flexion deformity.

### Tuberculous Disease of Ankle and Tarsus

In reviewing the end-results and treatment of tuberculous disease of the ankle and tarsus, Mitchell<sup>53</sup> arrived at some very definite conclusions. Adults with tuberculosis of the ankle frequently die with tuberculous infection elsewhere. In 23 cases treated conservatively, this was true in 35 per cent. No adult who had an early amputation developed a sec-

ondary lesion. In 14 cases with early amputation, 13 were living and well after several years. The benefits of the amputation were obvious, *i. e.*, (1) short disability, (2) the primary lesion was removed and secondary infection prevented; (3) worry and mental changes were avoided; (4) the mortality was lower; (5) the hospital expenses were less.

The following plan of treatment had been devised:

Adults over 45 years of age have an amputation through the upper tibia.

Subjects 17 to 35 years should have 6 months of conservative treatment. If the progress is arrested for more than 3 months, then amputation should be done.

Subjects from 35 to 45 years should have amputation at once if there is any case of doubt.

In children the care should always be conservative.

### Gonorrheal Arthritis

**Treatment**—An analysis of the treatment in 200 cases was made by Culp<sup>54</sup> at the Johns Hopkins Hospital. All cases were proven of gonorrheal origin. The criterion of the end-result was the unimpaired function of the joint. There were 45 chronic, 50 subacute, and 105 acute cases which were divided into 13 groups according to method of treatment. Only 3 types of therapy gave results worth recording. These were fever therapy, intravenous injections of mercurochrome and sulfanilamide. Of 19 patients given *fever therapy*, 53 per cent were markedly improved or well. Most of these received but 1 session of fever. Cures were effected in the chronic as well as in the acute cases. Several patients had severe reactions and 1 died while undergoing treatment. Of 29 subjects receiving *intravenous injections of mercurochrome*, 69 per cent were well or markedly improved. Excellent results were obtained in chronic

as well as the acute cases. The method of treatment consisted of  $\frac{1}{2}$  ounce (15 cc.) 1 per cent mercurochrome followed at intervals of 3 to 4 days by  $4\frac{1}{4}$ ,  $4\frac{3}{4}$ ,  $5\frac{1}{4}$  drams (17, 19, and 21 cc.), respectively. A rise in temperature following the intravenous administration was regarded as a favorable therapeutic reaction.

**Sulfanilamide** was used in 22 subjects; 60 per cent were well or markedly improved. In the few subacute and chronic cases in this group, little or no improvement was recorded. Twenty grains (1.3 Gm.) of sulfanilamide were administered every 6 hours with *sodium bicarbonate* for 2 weeks. This generally maintained the blood level at 8 mg. per 100 cc., which was considered optimal for response.

### Degenerative Arthritis of Knee-Joint

**Surgical Treatment**—In 20 cases of degenerative arthritis of the knee-joint, Haggart<sup>55</sup> has removed the patella, done a partial synovectomy, and removed the fat pad and menisci, if the latter showed degenerative changes. One case was reported as a failure. It was believed that this subject had an unrecognized infectious arthritis, as shortly following the surgical procedure he manifested other joint involvement. The cases selected were those of proven degenerative arthritis by clinical and x-ray examinations and were past the third decade. They generally gave a history of having sustained severe trauma to the knee in earlier life. They were usually overweight. The musculature of the extremities was often inadequate. They frequently had increase in synovial fluid. There was hyperplasia of the synovial membrane. Crepitation beneath the patella on palpation during motion was a common observation. Passive motion of the patella was painful. There was a

persistent flexion deformity, with pain reference to the anterior aspect of the knee-joint. The x-rays consistently showed degenerative changes of the patella even in the absence of arthritic manifestations in other parts of the joints. Rarely was the degree of degenerative change in the patella entirely revealed by the x-ray film

Treatment was the *excision of the patella* by means of a midline or median parapatellar incision. The patella was dissected from beneath the tendon, the tendon resutured to itself or the capsule by means of interrupted silk sutures. *Compression bandage* and a *plaster cast* for immobilization were applied. The latter was removed at the end of the seventh day. The leg was then suspended by means of an elastic cord from a *Balkan frame* to the ankle. Progressive *exercises* then were instituted. All cases were given intravenous *pentothal anesthesia* and *manipulation* carried out the third week following operation. The author claims this caused no reaction and the range of motion rapidly increased.

### Injury to Femoral Articular Cartilage by the Medial Meniscus

Smith and King<sup>56</sup> described 9 subjects who presented symptoms and signs indicative of a tear or gross displacement of the medial meniscus. At the time of arthrotomy, the medial meniscus was found intact but somewhat more mobile than normally. On the articular surface of the medial femoral condyle there was a well defined depression which corresponded in position and outline to the anterior portion of the medial meniscus. From the periphery of the condyle, a film of vascular tissue encroached upon the defects. When the knee was extended, the anterior portion of the medial meniscus fitted perfectly into the depres-

TABLE V  
COMMON CAUSES OF INEQUALITY OF  
LEG LENGTH

Conditions	Lengthen- ing	Shorten- ing
Poliomyelitis	—	+
Chronic bone infections	+	—
Tuberculosis of hip	—	+
Tuberculosis of knee	+	+
Epiphyseal injuries	—	+
Congenital dislocations	—	+
Tumors. . . .	+	—
Hemiatrophy	—	+
Hemihypertrophy	+	—
Congenital anomalies	+	+
Malunited fractures	—	+

sion. The lesion did not have the appearance of an osteochondritis dissecans. No loose bodies were found in the joint.

In each case a history of a twisting injury was given. This was followed by an effusion, pain was localized to the medial aspect of the joint, tenderness was elicited along the medial condyle; a limitation of flexion or extension was found in all cases. Instability of the knee was noted when climbing and descending stairs.

In all subjects symptoms had persisted from 1 to 24 months prior to operation. At the time of *arthrotomy*, the medial meniscus was removed routinely. Nothing was done to the defect in the condyle. The cases had been followed postoperatively for an average of 3 years, 7 subjects reporting normal knees and 2 were greatly improved.

Discrepancy in leg length, according to Wilson and Thompson,<sup>57</sup> is due to either a retardation of growth in 1 extremity or an overgrowth in the other. The most common cause of inequality of leg length is poliomyelitis.

There have been 2 ways of approaching the problem of leg inequality: *First*, changing the rate of growth. This has been attempted by stimulation of growth in the shorter extremities or retardation

of the growth in the longer extremities. Increase in longitudinal growth of growing bones had been observed both clinically and experimentally following fracture. It was believed by Ferguson that the interruption of the metaphyseal blood supply caused a hyperemia in the epiphyseal region which resulted in in-

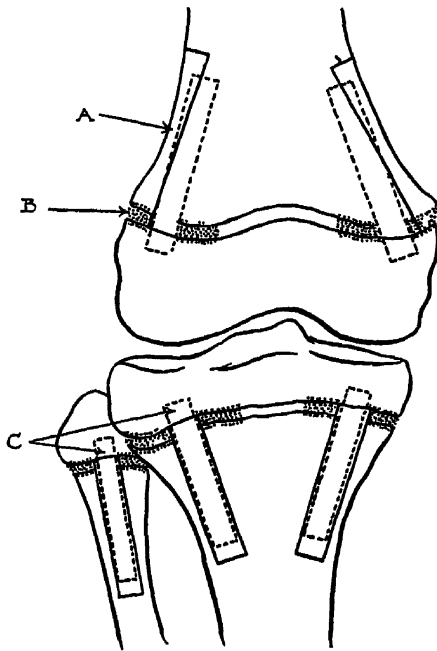


Fig. 37—Diagram of operative technic for epiphysiodesis. A, Bone removed for graft; B, area of epiphyseal cartilage curetted and cauterized; C, replacement of graft, with cartilage removed, across epiphyseal line. (Wilson and Thompson · Ann. Surg.)

crease in the growth rate. An attempt was made to apply this observation clinically by *drilling the cortex of long bones* and *curetting across the medullary cavity in the metaphyseal region*. Very little success was met with by the use of this method.

**Lumbar sympathectomy** was advocated by Harris to produce an increased blood supply in the short extremity. About 50 per cent of the cases treated in this manner showed a decrease in the discrepancy of leg length. The growth in the short extremity in cases of poliomyelitis was not stimulated to the extent

TABLE VI  
APPROXIMATE PROPORTIONAL GROWTH AT THE  
EPIPHYSES OF THE LOWER EXTREMITY

Upper femoral epiphysis . . .	15%
Lower femoral epiphysis.....	35%
Upper tibial epiphysis.. . .	30%
Lower tibial epiphysis . . . . .	20%

observed in normal legs of children upon whom the operation had been performed for Hirschsprung's disease. Wilson and Thompson had retarded the growth in the longer extremity in 34 subjects by doing an *epiphyseal arrest* (Fig. 37). They have had no postoperative infection or deformity as a result of this procedure. The technic was as follows:

- 1 The medial and lateral sides of the lower end of the femur or upper end of the tibia and fibula are exposed through separate incisions.
- 2 Bone grafts, about 1 x 4 cm. in size, are removed from the diaphysis. These extend as far as, but not across, the epiphyseal cartilage plate.
- 3 A large area from both the medial and lateral aspects of the cartilage disc is removed with a chisel or curet.
- 4 The curetted area is cauterized with the diathermy cautery.
- 5 The grafts are replaced, countersunk beneath the cortex of the diaphysis, and driven across the epiphyseal line into the cancellous bone of the epiphysis.

The authors considered each patient separately. The number of epiphyses to be blocked in the long leg was decided by the subject's previous rate of growth, expected growth, age, height, and discrepancy in leg length. Measurements of the subject's family were also taken into consideration when available. With the records of leg lengths over a period of years, which were available in most cases of poliomyelitis, the expected discrepancy in leg length could be estimated. If this discrepancy had not been increasing with growth, the existing discrepancy could be considered equal to

TABLE VII  
REPORTED RESULTS OF LEG LENGTHENING OPERATIONS

Author	Number of Lengthening Operations		Average Length Gained (Inches)	Complications Reported								
	Tibia and Fibula	Femur		Protrusion of Fragments or Skin Necrosis	Infection and Osteomyelitis	Delayed Union	Non-union	Fracture	Nerve Injury	Foot Deformity	Death	Failure to Gain Length
Abbott	48	25			2			7	3	Many	0	
Stephenson and Durham	15	2		2	3							
Carrell	21	7								1		3
Brockway	41	5	1 9 ins.	5				2				
Janes	5		2.25 ins		3		1					
Moore, J. R.	10				0	?			0	2		
Compere		5			4	1	2		1		1	?
Bosworth	19		1.9 ins.	2	2	3	4			6		
Alcorn	37		1 5 to 2 ins.									4
Haboush and Finkelstein	17			4	6	1	2			2		
Present report	11	2	1 9 ins.	5	2		3	1	1	3	0	0
Totals	224	46	2 ins.	18	22	5	12	10	5	14 -	1	7

the expected discrepancy. When the rate of growth in the longer leg had been greater than in the shorter leg, the increase in discrepancy would continue in proportion. By dividing the expected discrepancy in leg lengths by the amount of expected growth, the percentage of growth to be eliminated could be calculated. The authors recommended if the proportion was less than 25 per cent that operative treatment be delayed. If it was between 25 and 60 per cent, blocking of the upper femoral and upper tibial and fibular epiphyses should be done. If it was more than 60 per cent, all the epiphyses at the knee should be arrested. If it was more than 70 per cent equalization of leg length by this means could not be obtained.

For subjects under 10 years of age it was recommended that the growth of a single epiphysis be stopped, since another epiphysis could be fixed 1 or 2 years later if the growth in the longer leg was not as great as had been expected.

In comparing the result of 14 patients, averaging  $12\frac{1}{2}$  years of age at time of

operation, who had been observed from 1 to 4 years, it was found that 50 per cent of these showed a lessening of discrepancy of 1 to  $1\frac{3}{4}$  inches; 20 per cent of  $\frac{1}{2}$  to 1 inch; in 15 per cent, the discrepancy remained the same; and in 15 per cent the discrepancy increased slightly in spite of the operation.

The *second* method taken into consideration by the authors was that of *surgical reconstruction* by the means of bone lengthening of the shorter extremities or bone shortening of the longer extremities. In the 224 cases of bone lengthening reported in the literature, including the 11 cases of the authors, there were many serious complications in gaining a length of 2 inches (SEE: Table VII).

*Bone shortening operations of the longer extremity*, of which 100 had been reported by various surgeons, produced a uniformly good result with practically no complications. The authors concluded that this latter procedure was the method of choice when growth was well established.

### Claw-Foot

**Classification**—Claw-foot (pes cavus, hollow-foot), according to Cole,<sup>5</sup> may be classified in 4 grades, depending upon the amount of cavus deformity. In a mild grade, the cavus disappears when weight is placed on the foot. As the severity increases, the deformity becomes

location of the metatarsal phalangeal joint and contracture of the plantar structure, but may become arrested in any of the above mentioned stages.

**Etiology**—The deformity is explained as a result of weakness or interference with certain muscle functions of the foot. This condition is frequently accompanied

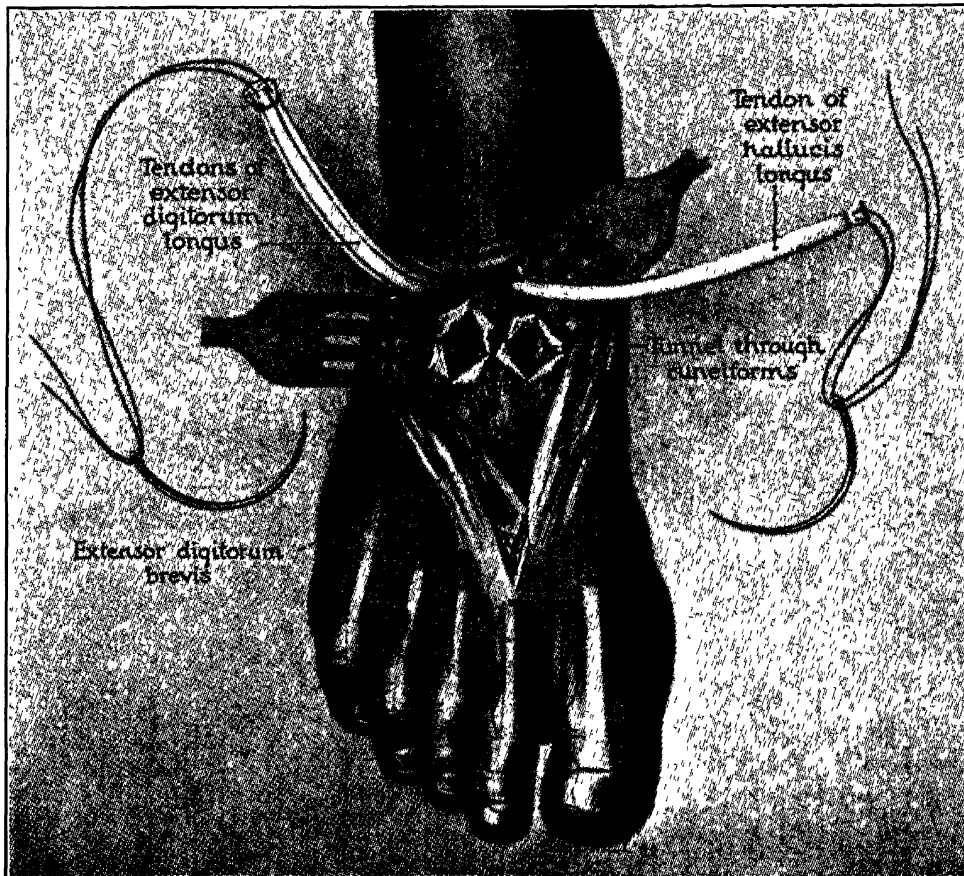


Fig 38—Tendons have been cut and the 4 slips of extensor digitorum longus held together in 1 bundle by suture of silk or chromic catgut. Tendon of extensor hallucis longus has similar suture attached to it. Tunnel in cuneiform bones has been drilled after periosteum has been scraped away from crucial incisions (Cole: J Bone and Joint Surg.)

more fixed and the heightened arch and the cocked toes do not disappear on weight bearing. As growth takes place, the tarsal bones of the foot become deformed. The deformity does not progress necessarily to the markedly deformed foot with the excessively high arch, large calluses or ulcers under the metatarsal head, hammer-toes with dis-

by a spina bifida occulta in the lumbosacral region. It is a common deformity in poliomyelitis cases. It appears in certain myelodysplasias, Friedreich's ataxia, multiple sclerosis and progressive muscular dystrophies.

The mechanism of the deformity could not be clearly explained. Three attributabel factors are (1) a weakness of the

interossei, lumbricalis and other intrinsic muscles of the foot; (2) weakness of the tibialis anticus muscle without involvement of the toe extensors; (3) a strong pulling or poorly opposed peroneus longus muscle.

**Treatment**—This depends upon the grade of the deformity. In the *early or*

a *night splint* with a bar to bring pressure back of the metatarsal heads.

In the *second group*, where the clawing is fixed but no bony deformity is apparent, a *plantar fasciotomy with stretching of the foot* is sufficient. In slightly more resistant cases, the *plantar structures* must be *freed from the os*



Fig. 39—Tendons shown in Fig 38 have been passed through tunnel in cuneiform bones, the extensor digitorum longus bundle from the lateral to the medial side, and the extensor hallucis longus in opposite direction. Tendons held in place by interrupted sutures, the distal one on each side passing through the periosteum. Through a small medial incision the interphalangeal joint of great toe is curetted in order to initiate ankylosis (Cole: J. Bone and Joint Surg.)

*mild stage* of the deformity a contracture of the plantar structures, cavus and clawing of the toes can be minimized. The routine advocated was daily *manipulations* to flatten the arch and stretch the plantar structures, *exercises* to strengthen the dorsi flexors of the foot without using toe extensors, the use of an *anterior arch bar in the shoe* and

*calcis*. This is followed by a *plaster-of-Paris bandage* for 3 weeks and then physiotherapy, consisting of the above mentioned *exercises*.

In the *third group* of cases, it is necessary to prevent the recurrence of the deformity. This consists in *transplanting the tendon* of the extensor hallucis longus muscle and the 4 tendons of the



extensor longus digitorum muscle into the cuneiform bones. These give additional reinforcement to the tibialis anticus in dorsiflexing the ankle. The procedure of transplanting these tendons into the heads or necks of the metatar-

In the *fourth group* of cases, a bone deformity exists. It is necessary to remove a wedge of bone. The author advocates that a wedge be removed through the scaphoid cuneiform joint and the cuboid in order not to interfere with the

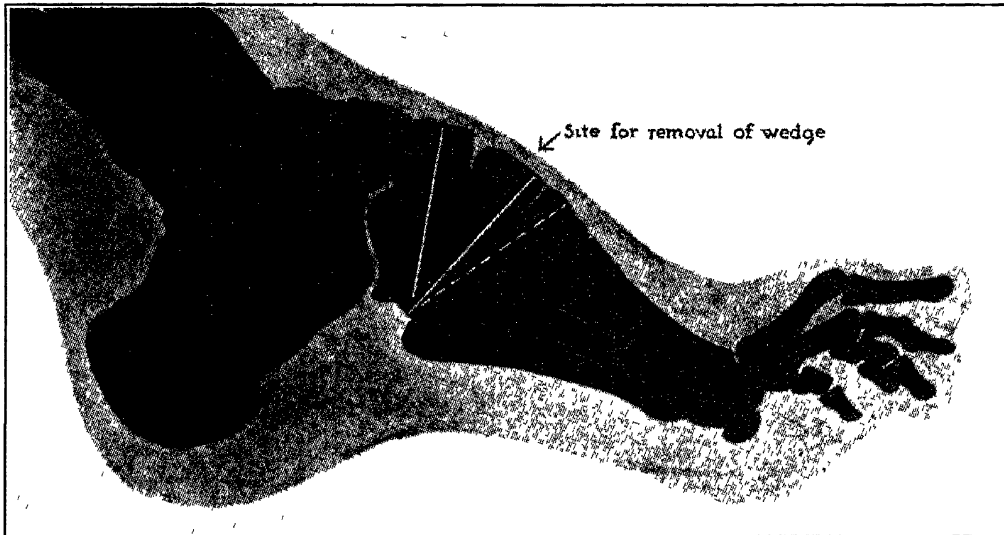


Fig. 40—Diagrammatic representation of foot to show location of wedge in anterior-tarsal-wedge osteotomy. Note that proximal cut is anterior to midtarsal joint (Cole: J Bone and Joint Surg)

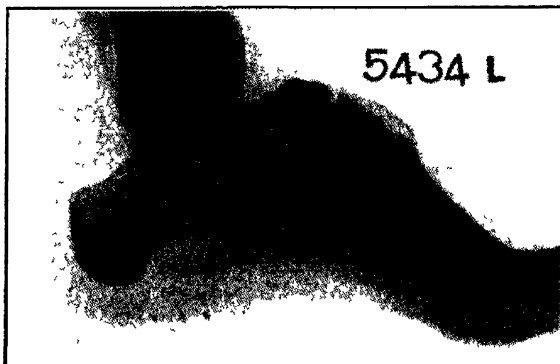


Fig. 41, A — Roentgenogram showing marked bone cavus before operation. (Cole: J. Bone and Joint Surg)

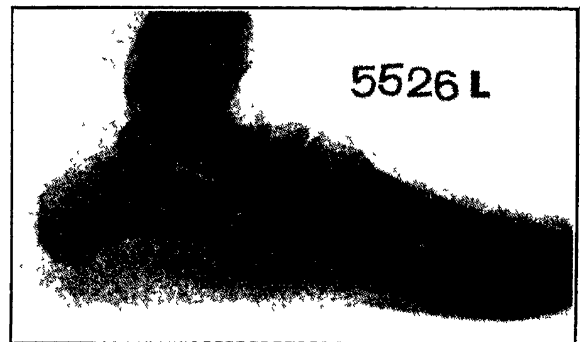


Fig. 41, B—Roentgenogram after plantar fasciotomy and anterior-wedge osteotomy. (Cole: J Bone and Joint Surg)

sals fails to overcome the deforming tendencies (Figs. 38 and 39). After severing the extensor longus hallucis tendon, it is necessary that the distal phalanx of the *toe* be *arthrodesed* in order that a plantar flexion of the distal phalanx should not exist.

subastragalar motion (supination, pronation) or abduction or adduction of the forefoot (Figs. 40, 41A and 41B). Following the *wedge tarsectomy*, the cut tarsal surfaces are opposed and a *plaster-of-Paris bandage* is used for immobilization for 8 weeks. Weight

bearing is then started without support. With the corrected cavus, the author claims that the toe deformity will generally be overcome spontaneously.

### Congenital Flat-Foot

**Treatment** — White<sup>6</sup> claims that the excessive length of the astragalar neck

of 1 or more tarsal joints, the author has ingeniously devised a procedure which removes a wedge from the medial aspect of the astragalar neck and reinserts this wedge on the lateral border of the os calcis (Fig. 42). The operation has been performed on 18 subjects. It was recommended that the heelcord

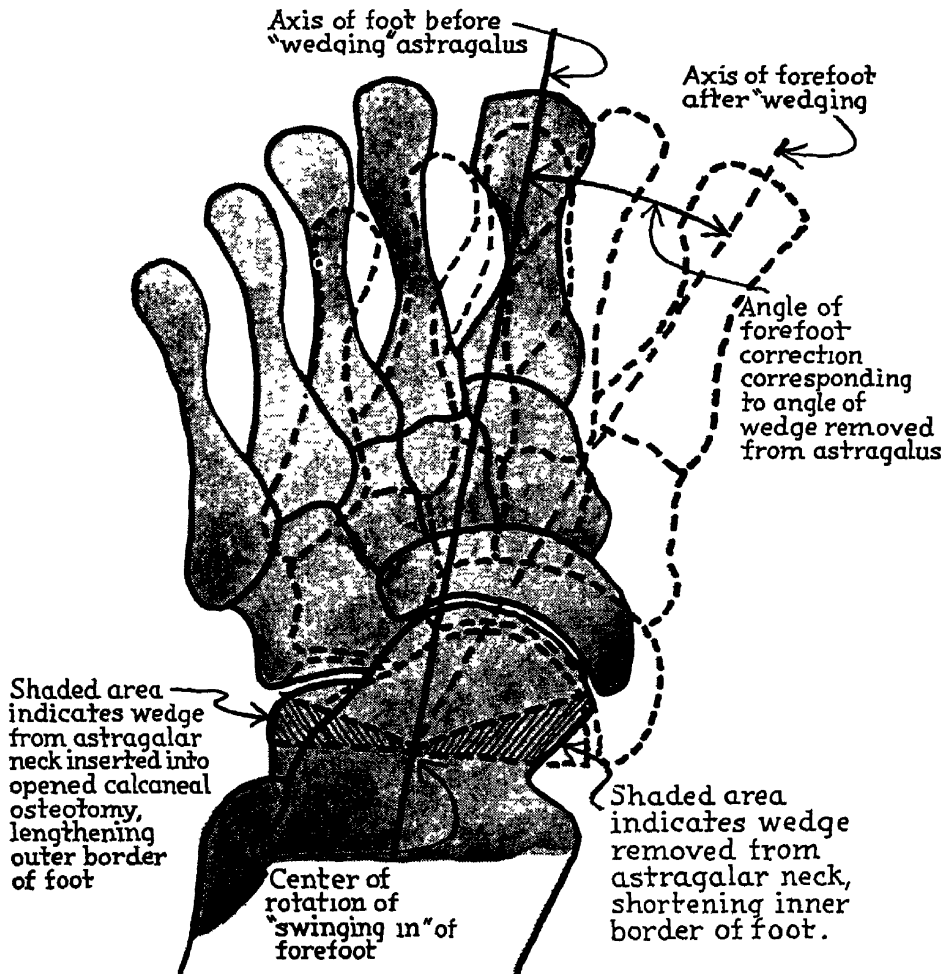


Fig. 42—Tracing of roentgenogram of a severely pronated foot suitable for surgical correction. Dotted outline shows position of "forefoot" after closure of wedge removed from astragalar neck, which is inserted into opening made by calcaneal osteotomy. The transverse osteotomy must be carried all the way across the astragalar neck, and the anterior one to complete the wedge must be directed toward the "center" of the foot at this point ("center of rotation" in the tracing). (J. W. White. J. Bone and Joint Surg.)

is responsible for a certain type of flat-foot. This is similar to the underdevelopment of the inner border of the foot which occurs in a club-foot. Since most operations for correction of the flat-foot have been accomplished at the sacrifice

be lengthened if it was found to be short at time of operation. Feet were *immobilized in plaster-of-Paris* for 2 months. This was followed by a *swung-in shoe* with  $\frac{1}{8}$  inch extra wedge on the inner side of the heel for

the first 6 months. *Exercises* then were carried out, directing the mobilization of the foot and strengthening of the tibial group of muscles, immediately after the removal of the cast.

### Traumatic Dislocation of Tendon of Biceps Brachii Muscle

Dislocation of the tendon of the biceps brachii muscle are believed by Abbott and Saunders<sup>7</sup> to be due to accidents which cause forcible lateral rotation of the arm. They consider some underlying attritional change to be the etiological cause. The injury was followed by local pain and swelling, with disability of the shoulder. The latter was particularly marked by the limitation of forward flexion and adduction. With the elbow held in flexion and the forearm actively supinated against resistance, pain was produced in the shoulder. Locally, there was swelling and tenderness over the bicipital groove. On passive abduction and external rotation of the shoulder, a definite snapping sensation could be obtained at times. In the 6 cases operated, the tendon was displaced over the lesser tuberosity. It was believed that satisfactory results could be obtained by *replacing the tendon in its groove*, holding it by a *strip of fascia* from either lip of the bicipital groove.

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## SYMPATHETIC NERVOUS SYSTEM

*Edited by* PAUL G. FLOTHOW, M.D., M S

### THE AUTONOMIC NERVOUS SYSTEM: GENERAL ANATOMY AND PHYSIOLOGY

*By* ALBERT KUNTZ, Ph.D., M.D.

**Introduction**—The most significant contributions to knowledge of the anatomy of the autonomic nervous system reported during the past few years relate mainly to the origin of the autonomic ganglion-cells, the intimate structure and organization of the automatic ganglia, the structural characters of the peripheral terminal mechanisms, and the central autonomic centers and conduction pathways. Additional anatomical data regarding the innervation of certain of the internal organs and the blood vascular system also have become available. The most significant physiological contributions are related to the behavior and properties of autonomic axons, the chemical mediation of nerve impulses, the functional classification of autonomic nerve-fibers, autonomic control of effectors and autonomic reflex activity.

#### **Anatomy**

**Histogenesis of Autonomic Ganglion Cells**—The results of experimental embryological studies reported by Raven and by Jones<sup>1</sup> corroborate the earlier finding of Kuntz that cells are displaced from the neural tube along the ventral nerve-roots and the communicating rami

into the sympathetic primordia where they become differentiated into ganglion-cells. Sympathetic ganglion-cells of neural crest origin are not precluded, but Jones<sup>1</sup> has shown that many of the cells which are displaced distally along the dorsal nerve-roots become differentiated into neurilemma.

**Autonomic Reflex Arcs**—The autonomic nerves are essentially efferent, but reflex arcs involving only autonomic neurons have long been known to exist in the enteric plexuses. Data reported by Kuntz<sup>2, 3</sup> support the assumption that the celiac and inferior mesenteric ganglia also include reflex connections. Axons which terminate in these ganglia in relation to ganglion-cells remain intact following degeneration of the preganglionic fibers of spinal nerve origin. Persistence of intact fibers in the distal segments of mesenteric nerves, following their division, supports the assumption that axons of enteric origin enter the celiac and superior mesenteric ganglia and effect synaptic connections with ganglion-cells. This assumption is further supported by the demonstration of inhibitory reflex responses in the proximal segment of the transected colon to dis-

tention of the distal segment following decentralization of the inferior mesenteric ganglia.

**Enteric Plexuses**—The innervation of the gastrointestinal tract has been the subject of several recent investigations, the results of which have added little to the knowledge of the structure of the enteric plexuses. Stöhr<sup>4</sup> has challenged the current conception of the structure of the autonomic system and advanced the theory, based in part on his studies of the enteric plexuses, that the autonomic ganglion-cells do not represent separate morphological units but constitute a syncytial structure, and that functional contacts are made with effector tissues through a terminal reticulum without clearly defined terminal processes. Boeke<sup>5, 6</sup> advanced further data bearing on the structure of the sympathetic ground plexus which he previously described in the walls of the enteric canal as well as in other parts of the body. His description of this structure conforms only in part to Stöhr's description of the terminal reticulum. He regards the ground plexus as the structure through which the autonomic nerves effect their peripheral functional contacts but concedes the individuality of the autonomic neurons.

Leeuwe advanced certain data in support of the theory that the interstitial cells of Cajal, associated with the enteric plexuses, are primitive neurons. He also claimed to have observed syncytial connections of these cells with the ordinary ganglion-cells in the myenteric and submucous ganglia. Meijling<sup>7</sup> also interpreted certain findings of his own as supporting the theory that the interstitial cells are primitive nerve-cells. Li,<sup>8</sup> who carried out an intensive study of the interstitial cells in the wall of the small intestine, supported the point of view advocated by Catel, according to which the

gastrointestinal musculature is innervated through 3 systems, *i. e.*, (1) the extrinsic nerves, (2) the intramural ganglion-cells incorporated in the ganglia of the myenteric and the submucous plexuses, and (3) the interstitial cells. The inner layer of the circular muscle, according to Li, is particularly rich in interstitial cells. He regards this layer as a neuromuscular mechanism which probably bears a definite relationship to irritability, conduction and rhythmic contractions, and plays a major rôle in the ordinary activities of the gastrointestinal tract in the absence of regulatory influence of the extrinsic nerves.

**Innervation of Biliary System**—The innervation of the biliary system has been studied in detail particularly by Sabussow and Ssuslikow and by Alexander.<sup>9</sup> According to their findings, numerous small ganglia occur in the hepatic portal and the walls of the cystic and common bile-ducts, all of which receive preganglionic vagus fibers. The sympathetic fibers which supply the biliary musculature are derived mainly from the celiac ganglia. The intramural nerves of the biliary tract comprise an adventitial, an intramuscular, and a subepithelial plexus. The structural pattern of these plexuses is similar to that of the enteric plexuses.

**Hypothalamic Autonomic Centers**—New data regarding the anatomical relationships of the hypothalamic autonomic centers have been reported by various investigators, including Clark,<sup>10</sup> Ranson and Magoun,<sup>11</sup> Griffiths<sup>12</sup> and Ingram.<sup>13, 14</sup> These centers involve most of the hypothalamic nuclei. Most of the neurons in the nuclei in question, furthermore, contribute fibers to the descending conduction pathways. Since the impulses conducted by these fibers are destined to reach preganglionic efferent nuclei, the neurons of which they are the

axons may be classified as central visceral efferent neurons. These neurons in general possess common cytological characters by which they may be differentiated from central neurons of other functional categories (Kirgis<sup>15</sup>).

#### **Autonomic Conduction Pathways**

—The conduction pathways through which impulses are conducted downward from the hypothalamic autonomic centers have been investigated particularly by Ranson and his collaborators. The major findings, as summarized by Magoun,<sup>16</sup> support the conclusion that the descending pathways include some long fibers and many short ones arranged in relays. Most of the fibers which descend from the diencephalic autonomic centers emerge from the lateral hypothalamic area. They traverse the central and tegmental areas of the mesencephalon and the tegmental area of the pons. In the medulla oblongata they lie mainly in the lateral portion of the reticular formation, and in the spinal cord, in the anterior portion of the lateral funiculus. Most of the fibers are limited to one side, but some cross the median plane in the brain stem or at lower levels in the spinal cord.

**Respiratory Centers** — New data bearing on the respiratory centers and the conduction pathways descending from them have been reported by Pitts.<sup>17</sup> According to his findings, the inspiratory center is localized in the inferior reticular nucleus; the expiratory center in the dorsal reticular formation in the medulla oblongata. The descending pathways from both these centers traverse the anterior and anterolateral funiculi in the spinal cord.

#### **Physiology**

**Properties of Autonomic Nerve-Fibers**—The physiological properties of autonomic nerve-fibers have been stud-

ied by several investigators, including Grundfest and Gasser,<sup>18</sup> Graham,<sup>19</sup> Maltesos and Schneider,<sup>20</sup> and Bishop and O'Leary.<sup>21</sup> The results of these studies support the classification of autonomic axons in several categories which differ both in threshold of stimulation and qualitatively. Some degree of specificity of autonomic fibers, therefore, is indicated.

**Functional Classification**—Data reported by Cannon and Lissák<sup>22</sup> support Dale's proposed classification of autonomic neurons into adrenergic and cholinergic groups. The results of previous studies had shown that stimulation of some autonomic neurons results in liberation of an adrenin-like substance at the peripheral junctions of their axons, whereas stimulation of others results in liberation of an acetylcholine-like substance at the neuro-effector junctions. The former neurons are now known to contain adrenin but not acetylcholine; the latter to contain acetylcholine but not adrenin.

**Chemical Mediators**—The nature of the chemical mediators effective at the autonomic neuro-effector junctions has engaged the attention of not a few investigators. The data reported during the past few years firmly establish the concept of humoral factors in transmission at the neuro-effector junctions, but do not warrant definite conclusions regarding the exact nature of the humoral substances. Data advanced by Luco and Lissák<sup>23</sup> support the assumption that activation of sympathetic fibers after degeneration of the divided preganglionic axons elicits liberation of adrenin-like substance in greater concentration than activation of the corresponding fibers on the normal control side. Goffart<sup>24</sup> and Goffart and Bacq<sup>25</sup> likewise have reported an increase in the acetylcholine content of the gastrointestinal tract fol-

lowing degeneration of the divided vagus nerves.

**Synaptic Transmission**—Transmission of nerve impulses at the synapses in autonomic ganglia also has engaged the attention of various investigators. Both electrical and humoral transmission have been advocated. Those advocating the electrical theory support the assumption that the mechanism of transmission across the synapse is essentially similar to that of propagation along an axon. Those advocating the humoral theory support the assumption that synaptic transmission is accomplished by a qualitatively specific process. According to the electrical theory, the presynaptic action potential is the transmitter. According to the humoral theory, the presynaptic action potential is inadequate for postsynaptic stimulation, but is concerned mainly or exclusively with the liberation of the mediator which is an acetylcholine-like substance. According to the electrical theory, this substance serves mainly to counteract fatigue and exerts a local vasodilator influence. It has also been regarded as a nonspecific metabolic product (Lorente de Nó, 26) and as a regulator of transmission (Schaefer and Haass<sup>27</sup>). According to Coopée and Bacq,<sup>28</sup> acetylcholine is indispensable for transmission through a ganglion, but they do not regard this conclusion as implying that the electrical theory of synaptic transmission should be discarded. Data advanced by Lanari and Rosenblueth<sup>29</sup> support the assumption that the process of transmission at ganglionic synapses is essentially similar to that at the neuro-effector junction. Failure of transmission during fatigue and the early stages of Wallerian degeneration of preganglionic fibers probably are due exclusively to insufficiency of acetylcholine liberation. On the other hand, certain phenomena of

transmission cannot be adequately explained on the basis of humoral agencies alone.

**Reactions to Adrenin**—In studies reported by Malméjac, Donnet and Jonesco<sup>30</sup> adrenin produced only constrictor responses in the cutaneous vessels in dogs. Goetz<sup>31</sup> reported similar observations in both cats and dogs. In his experiments, the vasoconstrictor reactions in the paw were quite independent of changes in blood-pressure. Marked constriction was observed in the absence of appreciable change in blood-pressure. In other instances a rise in blood-pressure attained its maximum before any constriction in the paw became apparent. Goetz, therefore, concluded that the reaction of the cutaneous vessels is not of primary importance in producing the first rise in blood-pressure after the administration of adrenin and that adrenin plays its rôle in controlling the distribution of the blood rather than in augmenting blood-pressure.

**Vasomotor Nerves** — Forbes, Schmidt and Nason<sup>32</sup> reported additional data in support of the assumption that the cerebral vasodilator nerves are parasympathetic. Katz and Jochim<sup>33</sup> reported experimental observations which cannot be reconciled with the current teaching that the coronary vasoconstrictor nerves are parasympathetic and the coronary vasodilator nerves are sympathetic. According to their findings, the vagi include only coronary vasodilator fibers. These fibers are tonically active and are cholinergic. The sympathetic coronary innervation includes both adrenergic vasoconstrictor and adrenergic vasodilator fibers, both of which are tonically active. The effects of stimulation of the sympathetic coronary nerves were found to be predominantly vasoconstrictor. According to these findings, the coronary nerves react similarly to

other sympathetic and parasympathetic nerves; in other vascular areas where both are present, the action is the same.

Kabat<sup>34</sup> demonstrated vagus cardiac accelerator fibers predominantly in the right vagus. These fibers are adrenergic and are not excited reflexly by stimulation of the carotid sinus.

**Innervation of Pancreas**—Babkin, Hebb and Sergeyeva<sup>35</sup> reported external secretory activity of the pancreas, in response to stimulation of the splanchnic nerves, comparable to that elicited by stimulation of the vagal secretory fibers. Such secretory activity could not be elicited by injection of adrenin, but acetylcholine could be detected in the venous blood in the gland after splanchnic stimulation. The authors therefore concluded that the splanchnic secretory fibers in question are cholinergic. The results of tests with nicotine also support the assumption that there is a peripheral relay beyond the celiac ganglion. The detection of acetylcholine in the venous blood of the pancreas following splanchnic stimulation is in disagreement with the observations of Gayet, Minz and Quivy,<sup>36</sup> who detected acetylcholine in blood from the stomach and occasionally from the intestine but never from the pancreas.

Sergeyeva<sup>37</sup> noted an increase in the  $\beta$ -cells when the cholinergic splanchnic fibers had been stimulated or the parasympathetic nerves had exerted a predominant influence as a result of previous removal of the abdominal sympathetic trunks. The  $\alpha$ -cells were increased in most cases in which the sympathetico-adrenal influence was predominant by reason of splanchnic stimulation or section of the vagi.

**Cortical Representation** — Additional data bearing on autonomic representation in the cerebral cortex have been reported, particularly by Crouch and

Thompson.<sup>38</sup> In their experiments on cats, dogs and monkeys, electrical stimulation of different points in the motor and premotor cortical areas resulted in activation of various autonomic effectors, but no well-defined cortical areas were found from which certain limited visceral reactions could be elicited. Areas which influence parasympathetic functions could not be separated from those which influence sympathetic functions.

**Reactions to Hypothalamic Stimulation**—Visceral responses to hypothalamic stimulation have been studied by numerous investigators. Wang and Harrison<sup>39</sup> reported activation of the urinary bladder through both the hypogastric and sacral autonomic nerves in response to stimulation of the anterior portion of the hypothalamus. Wang and his associates<sup>40</sup> also reported sympathetic gastrointestinal responses to stimulation of the hypothalamus anterior to the infundibulum, and parasympathetic enteric responses to stimulation of the hypothalamus at the level of the infundibulum or behind it. The descending pathways involved, according to Wang and Clark,<sup>41</sup> show no evidence of decussating fibers in the cervical, thoracic and upper lumbar segments of the spinal cord, but cross connections occur in the brain stem and in the lower lumbar segments of the cord. The decussation in the brain stem may be either multiple or diffuse. According to Harrison, Wang and Berry,<sup>42</sup> vasomotor impulses arising in the hypothalamus may descend on the same side or cross in the brain stem or in the spinal cord below the cervical segments. Crossing first in the brain stem and again in the spinal cord also has been demonstrated. The rôle of the hypothalamus in the regulation of body temperature and in the normal alternation of the waking and sleeping states has been emphasized by Ranson.<sup>43</sup> Destruction of



the posterior lateral portion of the hypothalamus results in somnolence and emotional stolidity.

#### **Mesencephalic Autonomic Center**

—A mesencephalic center which exerts an influence on the tonicity of the smooth muscle of the rectum has been described by Langworthy and Rosenberg.<sup>44</sup> Transection of the brain stem below the level of this center, in their experiments, resulted in abolition of the stretch responses in the rectum.

**Reflex Vasomotor Activity** — In experiments carried out on decerebrated animals Yi<sup>45</sup> observed that reflex lowering of blood-pressure, elicited by stimulation of several afferent nerves, was not abolished by cauterization of the myelencephalic pressor center, but disappeared following destruction of the depressor area around the obex. On the basis of his experimental results, he concluded that there is an independent reflex center in the medulla oblongata which inhibits sympathetic vasoconstriction. Downman and his associates<sup>46</sup> observed that maximal constriction in the paws could be elicited by stimuli which produced a rise, a fall, or no change in blood-pressure. In an experimental study in which the vasomotor reactions in the submaxillary gland, elicited by chemical stimulation of the carotid body, were studied, Bernthal and Motley<sup>47</sup> observed that in 9 dogs out of 11 these reactions were abolished by cervical sympathectomy, but residual reactions persisted in the other 2, which presumably were mediated through parasympathetic nerves.

In a study of the vascular reactions in the gastrointestinal tract elicited by localized cutaneous stimulation, Kuntz and Haselwood<sup>48</sup> recorded the vascular changes photographically and by means of the plethysmograph. Moderate cooling of the skin resulted in vasoconstriction and moderate warming of the skin

resulted in vasodilatation in the corresponding portions of the gastrointestinal tract in decerebrated cats. These records afford concrete evidence of the validity of a principle which has long been applied in the treatment of visceral and other deeply located lesions. The data obtained also afford evidence in support of the assumption that stimulation of the receptors involved in cutaneovisceral vasomotor reflexes probably is associated with changes in the tonic state of the cutaneous blood-vessels.

**Sensitization of Autonomic Responses**—The conclusion of Cannon and Rosenblueth that sympathetic nerves exhibit increased sensitivity to the stimulating action of acetylcholine following degeneration of the preganglionic fibers has been corroborated by data reported by Chauchard.<sup>49</sup> Youmans, Aumann and Haney<sup>50</sup> have shown that the intestinal musculature exhibits increased sensitivity to adrenin and other sympathicomimetic substances following section of its extrinsic nerves. Sympathetic denervation of the submaxillary gland, as reported by Simeone and Maes,<sup>51</sup> also results in increased sensitivity to adrenin, pilocarpine and acetylcholine.

In a study of the differences in sensitivity of various normal systems to acetylcholine, Tournade and Chardon<sup>52</sup> found that vasodilatation was obtained most easily. Next in order came secretion of adrenin, contraction of the spleen, and respiratory acceleration. Retardation of the heart required much larger doses than those which brought about the other reactions. Danielopolu and Marcu<sup>53</sup> also reported that the blood-vessels become sensitized to the vasoconstrictor action of adrenin by small doses of acetylcholine, whereas the responses to adrenin are reduced by larger doses of acetylcholine.

Sensitization of the vascular musculature in the affected area, following section of sympathetic fibers, to the adrenin normally present in the circulating blood has been observed in many clinical cases. Such sensitization probably is of relatively short duration. According to Simmons and Sheehan,<sup>54</sup> whose studies are based on clinical cases following sympathectomy, hypersensitivity of the vessels to adrenin reaches its maximum 8 to 10 days after operation and then gradually subsides. In some of their cases it had apparently disappeared after several months.

**Vascular Reaction Patterns**—According to Burton and Taylor,<sup>55</sup> the blood flow in the fingers fluctuates con-

tinually within relatively wide limits. Some of these fluctuations probably represent rhythmic changes in the vasomotor tonus. Others are due to various causes, including psychic factors. By the use of the photoelectric plethysmograph, Hertzman and Dillon<sup>56</sup> have recorded spontaneous waves in peripheral vessels. These waves usually appear as constrictions in the vessels of the extremities and dilatations in those of the head skin, but of varied character in those of the ear and nasal septum. They may or may not exhibit synchronism in different vascular areas. Most of these waves probably are due to vasomotor activity, but some appear to be due to activity of the smooth muscle locally and independently of nervous influences.

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## THERAPEUTIC CONSIDERATIONS IN DISEASES AND CONDITIONS RELATED TO THE SYMPATHETIC NERVES

By PAUL G. FLOTHOW, M.D., M.S.

**Introduction**—A vast amount of work has been done in the past year on the sympathetic nervous system, but the major part of this work has been on its anatomic, physiologic and chemical aspects. There has been a paucity of new clinical work in the literature. There is no question that the pendulum will swing back and forth with regard to various conditions considered under the sympathetic nervous system and the application of sympathetic surgery in these conditions. There is, also, no doubt that as time goes on there will be less and less new work reported each year. It is apparent that at the present time a decline is beginning to be seen in new clinical applications of sympathetic surgery, since the unexplored field is narrowing each year.

### I. Conditions Primarily Due to Vascular Disorders

**1. Vascular Disorders**—The treatment of vascular disorders in which the primary cause of vascular insufficiency is vasospasm still continues to be dominated by surgical excision of the proper sympathetic ganglia. It does seem, however, that the predominance of opinion in the treatment of obliterative vascular diseases is becoming less in favor of sympathetic surgery and more in favor of conservative measures, the latest of which has been the substitution of intermittent venous occlusion for the use of the previously popular *Paevex therapy*.

The fact that the medical management of vascular lesions, particularly of Buerger's disease, continues to be in a flux, and that one year a great deal is heard

about a certain type of therapy and the next year this therapy is found to be ineffective and is supplanted by another, leads to the conclusion that there is much wanting in all forms of therapy advised on a purely nonsurgical basis.

**Sympathectomy** continues to offer a great deal of benefit in all types of obliterative vascular lesions where there is a definite element of vasospasm present. There has been nothing particularly new published in the last year along these lines.

2. **Ainhum**—This is an interesting although a very uncommon condition. McKnight<sup>57</sup> has reported a case of ain-hum treated by *lumbar sympathetic ganglionectomy* with spectacular result. Ainhum apparently is a neurovascular disease of tropical origin, the etiology of which is unknown. The disease is characterized by a spontaneous amputation of the toes.

Simmons and Sheehan,<sup>54</sup> in reviewing their cases to determine the cause of relapse after sympathectomy performed for vascular lesions of the upper extremity, come to the following conclusion: First of all they have found that this relapse occurs when either type of operation is performed, *i. e.*, ganglionectomy or the preganglionic resection which has been the latest type of operation used in these cases. They conclude that the relapse is due to the fact that there is regeneration of nerve-fibers. They agree with Smithwick, Freeman and White that there is definitely a hypersensitivity of the blood-vessels to circulating adrenalin after sympathetic operations, and that this hypersensitivity is much less after preganglionic section than it is after postganglionic section. They felt, furthermore, that this sensitivity decreased with time after both types of operation, whereas the regeneration of fibers in-

creased with time and was the true cause of relapse.

3. **Chronic Ulcerations**—Homans<sup>58</sup> treats chronic ulceration of the extremities with edema and fungous infections which are resistant to medical treatment by *sympathectomy*, and obtains excellent results. The hot, dry skin which results from section of the sympathetic nerves is hostile to fungus growth, and the improved circulation aids in healing the ulcer.

4. **Thrombophlebitis**—Ochsner and DeBakey<sup>59</sup> and many others continue to treat thrombophlebitis very successfully by *novocainization of the lumbar or cervical sympathetic ganglia*.

## II. Conditions Due to Abnormal Physiology or Function of Organs

**Asthma**—Keeney<sup>60</sup> suggests that most asthmatic patients can be treated adequately medically, but that there is a small group of patients with chronic bronchial asthma who fail to obtain relief from any method of medical treatment. He states that in this group various operations have been suggested, *i. e.*, *unilateral sympathectomy*, *unilateral ganglionectomy*, *unilateral vagotomy*, and *unilateral and bilateral posterior pulmonary plexectomy*. He is, however, of the opinion that the operation of choice is bilateral posterior pulmonary plexectomy.

## III. Miscellaneous Conditions

1. **Essential Hypertension** — The question of surgical treatment of essential hypertension still occupies a great deal of attention among those interested in sympathetic surgery. The difference of opinion regarding the value of surgery in this condition continues to make itself very clearly felt. Those doing this type of surgery continue to be very enthusias-

tic and continue to report excellent results in their cases. The greatest enthusiasts for this type of treatment are The Mayo Clinic Group and the Michigan Group.

Peet, Wood and Braden<sup>61</sup> have recently reviewed 350 cases of essential hypertension treated by *supradiaphragmatic splanchnicectomy* and *lower dorsal sympathetic ganglionectomy*. They conclude that the operation of supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy is of great value in the treatment of hypertension. In their series of cases 86.6 per cent had postoperative relief of major symptoms, especially headache; 81.3 per cent had improvement or complete relief of incapacitation; and 51.4 per cent with adequate postoperative data had a significant reduction in the blood-pressure. Approximately one-half of these patients had pressures either reduced to normal or markedly reduced. Improvement in the ophthalmologic, cardiac and renal status following operation varied from 45 to 70 per cent of the cases studied.

They state that the *prognosis* is much more favorable in females than in males, and that the most favorable results are obtained in the group below 30 years of age. Following this period they seem to feel that the age of the patient is of minor importance as far as the results of the operation are concerned. This is, of course, in contradistinction to their previous reports and the reports of other authorities who feel that operation on patients over 50 years of age is not very often indicated. Apparently they have found that their cases in the upper age brackets have done on the average just about as well as those in the lower age brackets. They do not feel that marked fundus changes are a contraindication to the operation. They rate their mortality

3.4 per cent, and state that there are no specific untoward effects attendant on the operation. They conclude that since there is no other form of therapy which offers as good results as this type of surgical treatment, the surgical treatment of hypertension by their method offers the best prognosis of any form of therapy yet reported.

There are some essential differences between the *supradiaphragmatic* and the *infradiaphragmatic operation*, the major difference being that the former is largely preganglionic, certainly preganglionic to the celiac ganglion, while the latter operation is of necessity postganglionic if the celiac ganglion is removed. The advantage of the infradiaphragmatic operation is that it is possible to explore the adrenal glands in the course of operation which cannot be done by Peet's technic. The reason for this is that occasionally a tumor of the adrenal gland is apt to be found which is the cause of the hypertension. Another advantage of the infradiaphragmatic operation is its apparent greater safety than the supradiaphragmatic operation. Peet reports 3.4 per cent mortality, whereas The Mayo Clinic group have reported large series of cases without operative mortality.

The Reviewer's mortality in a much smaller series than either of these institutions is *nil* at the present time, with perhaps some 50 cases in the series.

**2. Arteriovenous Aneurism** — A very interesting report has been made by Plotkin<sup>62</sup> regarding the use of sympathectomy at a distance in certain operations for arteriovenous aneurism. He resected an arteriovenous aneurism in the popliteal space. Following this operation the leg was cold and pale, and assumed a cadaverous appearance, and it seemed that gangrene was inevitable. He, therefore, performed a *lumbar sympathetic ganglionectomy* on the affected

side, and immediately noticed that the limb resumed its normal state. It differed in no respect from the opposite one. While this is not entirely a new observation, it is most interesting and worth noting at this time.

The Reviewer has had a personal experience with this type of lesion, or at least a similar one. During the course of a cervicodorsal sympathectomy the subclavian artery was inadvertently severed in its first portion, and it was necessary to ligate both ends of the subclavian artery. He then proceeded with the operation of cervicodorsal sympathectomy, and while at the conclusion of the operation no radial pulse was palpable, there was no evidence whatsoever that there had been a ligation of the major artery to the arm. The arm was warm, dry and pink, and no trouble whatsoever ensued as a result of this ligation. It would seem, therefore, as the writer has advocated in the past, that in the event the necessity of ligation of a major artery with the consequent danger of gangrene arises, a prompt sympathectomy will no doubt avoid gangrene in almost every instance.

**3. Carotid Sinus Syndrome**—Rosier<sup>63</sup> reports a carotid sinus syndrome of the cerebral type. The features of this type of carotid sinus syndrome were sudden attacks of dizziness accompanied by headache and sensation of scintillation. Other symptoms, varying with the individual, were sudden facial skin discoloration, noise in the head or ears, cardiac pain, palpitation of the heart, dyspnea, loss of consciousness, vertigo on brusque movement of the head, temporary paresis of the arms and legs, and a bad taste in the mouth, etc. Bilateral compression of the carotid sinus induced the phenomena of dizziness, mental confusion, loss of consciousness and chronic spasm with even greater intensity than appeared in

the spontaneous attack. Medical management failing to relieve these patients, the author suggests *surgical denervation of the carotid sinuses*.

**4. Effect of Presacral Neurectomy on Childbirth**—Pearce<sup>64</sup> concludes (1) that presacral neurectomy has no bad influence on any part of the process of pregnancy, and (2) that in some patients the first stage of labor is painless and rapid, or else unobserved.

**5 Angina Pectoris**—White<sup>65</sup> reviews his work on the treatment of angina pectoris by *paravertebral alcohol injection*. He describes the technic of injection of the upper thoracic sympathetic rami and the cardiac nerves, and describes the safeguards which should be used during the injection to avoid intrathecal injection of alcohol. He reiterates the fact that the objection to this form of treatment sometimes advanced to the effect that stopping the pain of angina pectoris takes away the warning signal of the patient is unfounded. He states that an adequate warning is nearly always preserved, but that the patient must be warned that the cardiac reserve will not necessarily be increased. He concludes that in experienced hands paravertebral injection carries less risk, and is, therefore, applicable in a greater number of patients who suffer from anginal pain than is surgical resection of the necessary sympathetic nerves. This is in contradistinction to the opinion and the experience of the Reviewer.

After doing alcohol injection in some 30 patients without a single mortality, the Reviewer has had 3 deaths within the past 2 years following very soon after alcohol injection. One of these deaths occurred on the operating table, 1 within 6 hours, and the third some 4 days after injection. The latter case was found at post-mortem examination to have had a coronary thrombosis.

Since the Reviewer has been able to do a number of surgical resections in these cases without any untoward effects whatsoever, he feels that the *operative treatment* of angina pectoris should be very definitely considered in preference to the alcohol injection method. There is no question in his mind that there is tremendous shock when the alcohol is injected into the retropleural space, and he is sure that all who have used this treatment will agree with this statement. Using *pentothal sodium intravenous*

*anesthesia* he has been able to operate a number of severe cases of angina without any untoward effects, and up to the present time without mortality or anything that even caused worry in the way of operative complications.

It is the present opinion of the Reviewer that even the patient of advanced age is better able to stand the operative resection which carries practically no surgical shock than they are able to withstand the tremendous shock incident to the injection of alcohol.

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## SYMPATHECTOMY IN HYPERTENSION

By WINCHELL MCK. CRAIG, M.D., M.S., Sc.D.

Smithwick and his colleagues at the Massachusetts General Hospital are convinced that sympathectomy yields best results when the operation is (a) adequately complete, (b) preganglionic in type, (c) extensive enough to guard against future regeneration of interrupted pathways. In addition to the above, an operation for hypertension should include exploration of the kidney, the adrenal glands, and paravertebral region. Such an operation to be adequate should produce postoperatively a postural change in blood-pressure.

Smithwick<sup>66</sup> explained that in his hands the supradiaphragmatic and infradiaphragmatic and the celiac ganglionectomy proved inadequate and he devised a combination type of operation which allows a more extensive resection of the splanchnic nerves and thoracic sympathetic ganglia. Anatomically, he believes that rami from the sixth, seventh, eighth, ninth, and tenth thoracic nerves join the aortic plexus and if not divided, prevent a complete denervation of the splanchnic region. His segments of division of the rami and resection of the

sympathetic ganglion from above the ninth thoracic and below the first lumbar necessitate an incision which allows for both supra- and infradiaphragmatic exploration.

"Through a hockey stick incision, adequate exposure of the region can be obtained by resecting the twelfth rib. The upper portion is vertical, about 2 inches lateral to the midline, running up over the inner end of the eleventh rib. The lower portion curves laterally,  $\frac{1}{2}$  inch below and parallel to the twelfth rib. The sheath of the sacrospinalis muscle is opened vertically to below the twelfth rib, and dissection is then carried laterally following the skin incision through the deeper structures below and beyond the tip of the rib. The twelfth rib is removed from the transverse process to the lateral border of the sacrospinalis sheath. The twelfth intercostal artery, vein, and nerve are resected over a similar area. The diaphragm is divided from its lateral border to the spine, 1 inch below and parallel to the pleural reflection. The pleura is then separated from the thoracic cage up to the middorsal region. The kidney then is readily exposed and inspected. The adrenal gland is readily seen and explored. The sympathetic trunk and paravertebral region are exposed from the ninth dorsal to below the second lumbar ganglions. The great splanchnic nerve can be seen from its insertion in the celiac plexus upwards for vir-

DORSOLUMBAR SYMPATHECTOMY (Smithwick<sup>67</sup>)

Degree of Hyp. (Grade)	No of Pts	Fall in Blood-pressure				Symptomatic Improvement				Duration of Follow-up			
		No Signif Fall	To Normal	Normal Syst Elevated Diast.	Marked Fall Elevated Syst and Diast.	No Symptom	No Change	Improved	Unestimated	1-2 mos.	2-6 mos	6 mos 1 yr	1-2 yrs
I	8	1		4	3		2	3	3	2		3	3
II	4	1		2	1			2	2		2	1	1
III	10	3	2	2	3	2		3	5	1	5	3	1
IV	7	4		2	1	1	2	4		1	2	1	3
	29	9		10	8	3	4	12	10	4	9	8	8
			Good response in 75.8%										

tually its entire extent, with its important branches running to the aorta above the diaphragm. The greater splanchnic nerve is resected as high as the ramus coming from the sixth dorsal and the rami from the ganglionated trunk and to the aortic plexus. The lesser splanchnic is then removed and the sympathetic trunk from the ninth dorsal to below the first lumbar is removed. After this the diaphragm is resutured and the wound is closed in layers of silk. Intratracheal anesthesia is used. The operation is done in 2 stages between 1 and 2 weeks apart."

Smithwick began doing this operation in September, 1938, since which time he has operated upon approximately 60 patients who have been totally unselected other than on the basis that they would survive the operation, excluding those with advanced renal and cardiac failure

In a communication from Smithwick, he stated that Palmer has recently reviewed the early results extending from a few months to 2 years in about half of the patients that have been operated on, or 30 patients. The results have been based on significant changes in blood-pressure levels and improvement resulted in 75 per cent of the series. This improvement occurred in the following cases: 7 of the 8 cases in which the hypertension was grade I; 3 of the 4 cases in which it was grade II; 5 of the 10 cases in which it was grade III; 3 of

the 7 cases in which it was grade IV (malignant hypertension).

In Smithwick's experience this more radical type of sympathectomy has been followed by better results in the more severe type of hypertension and he is advocating it, although he urges more careful preoperative studies and selection of cases in which this operation is to be done.

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## THYROID GLAND SURGERY

By V. W. MURRAY WRIGHT, M.D.

### Hyperthyroidism

#### Present Status of Treatment—

Thompson<sup>1</sup> points out that there are 3 ways of treating patients with toxic goiter, *i. e.*, (1) by **subtotal thyroidectomy** following adequate preparation; (2) by medical measures alone, includ-

ing **iodine**; (3) by **Roentgen-ray therapy** of the gland. Ordinarily, medical measures alone have not proven satisfactory. In a few mild cases, either before or after the operation, the disease may be held in check by iodine until it disappears. The disease, however,



appears to run a certain course independent of the administration of iodine, and the mild cases may become severe, thus increasing the hazard of operation. The results of Roentgen-ray therapy are uncertain and a considerable period of time ordinarily must pass before its effectiveness can be determined.

**Roentgen-Ray Therapy** — When the condition has become unusually severe even with the intelligent use of iodine, adequate rest, and a high caloric diet (4000 to 5000 calories), Roentgen-ray therapy may be of value as a method of improving the *preoperative* condition of the patient. Following each exposure of the gland to Roentgen therapy a temporary reaction results with an increase in the severity of the disease. It becomes important, therefore, to use this form of therapy but once each week.

The dosage usually used is 300 Roentgen units at a distance of 50 cm. applied on alternate weeks to each lobe and part of the isthmus until a total of from 8 to 12 treatments has been given. The dosage must, of course, be adjusted for each patient, depending on the initial severity of the disease and the reaction to treatment. In severe cases the initial doses should not exceed 100 Roentgen units each. Due to reaction in the tissues of the neck, it is unwise to carry out operative procedures until 3 weeks have elapsed from the time of the last treatment.

**Digitalis**—This is frequently helpful in patients with auricular fibrillation and cardiac decompensation, although Thompson advises against starting the administration of digitalis in the post-operative period.

**Discharge from Hospital**—Supervision of the patient with toxic goiter does not conclude with the patient's discharge from the hospital. A periodic check-up to detect any complications

should be made at regular and frequent intervals. In approximately 70 per cent, the basal metabolic rate drops to within normal limits and remains there indefinitely. In 20 per cent a mild or moderate depression of the metabolism is observed and in 1 or 2 per cent marked myxedema may appear.

In 5 to 10 per cent of patients, *persistence* or *recurrence* of toxic goiter has been noted. True recurrences, however, are rare but do occur. These can be identified only by having an adequate follow-up program.

**Postthyroid or Recurrent Postoperative Hyperthyroidism**—Persistent or recurrent hyperthyroidism following thyroid surgery has ever been a vexing surgical problem. According to Berlin and Gargill,<sup>2</sup> the problem of persistent and recurrent thyrotoxicosis following apparently adequate subtotal thyroidectomy has been discussed ever since the surgical treatment of toxic goiter was standardized. Crile has advocated his dekineticizing operation of *bilateral denervation of the adrenals*. Others conceive the solution of the problem in *adequate thyroidectomy*. Scott advocates a *total thyroidectomy*. The authors studied 235 cases of toxic goiter in which operation was performed at the Beth Israel Hospital from 1932 to 1938. Whereas they found that the *incidence of persistence and recurrence was 5.1 per cent*, the Thompsons and Morris reported an incidence of *19.5 per cent* in a similar series of 190 cases. Although there is considerable variance between these authors' results, it should be noted that 1 of the reasons for the low incidence in the series of Berlin and Gargill is that a radical *subtotal thyroidectomy* was performed in most of their cases.

The factors probably responsible for persistence and recurrence in this series

have been found to be an *inadequate thyroidectomy*, the unique personality and fundamental imbalance of patients with exophthalmic goiter, frequent upper respiratory infections, and *psychic trauma* from marital infelicity or financial insecurity. Of late, many surgeons are appreciating the importance of these 2 latter factors and are giving attention to them postoperatively in conjunction with the family physician.

No case of either persistent or recurrent thyrotoxicosis has been observed following subtotal thyroidectomy for toxic nodular goiter.

Before resorting to a second operation, it must be remembered that the symptoms and signs of many patients with persistent and recurrent thyrotoxicosis can be controlled fairly completely by *iodine* medication, either alone or in combination with *Roentgen treatment*. The ideal treatment, of course, for recurrent and persistent thyrotoxicosis, especially when there is marked degeneration of thyroid tissue, is a *maximal or total excision of the thyroid remnants*. Such a procedure is likely to result in *postoperative myxedema*, but this can be controlled satisfactorily by *thyroid medication*. The incidence of permanent postoperative myxedema in this series was *only 3.9 per cent*, in spite of the fact that most of the patients had radical subtotal thyroidectomies.

Every patient who develops recurrent hyperthyroidism after a thyroid operation is an individual problem. Home or personal problems must always be examined into and diplomatically handled. In most instances, surgeons hesitate to perform a second operation for various reasons; also, the patient often refuses or delays the performance of a second operation. Whatever the cause may be, however, for

delayed surgery in any such case, the internist and the surgeon foremost should bear in mind that procrastination with this condition leads but to continuing and possibly *irreparable* cardiac damage which will leave the patient partially crippled even after delayed surgical and sociological intervention.

**Preoperative and Postoperative Treatment**—Toxic goiter is as different in its various clinical manifestations as it is in its pathological picture as described by Womack.<sup>3</sup> There is a vast difference between the young person with an acute fulminant exophthalmic goiter and an elderly individual with a mildly toxic nodular goiter. On the basis of this difference a number of authorities have assumed the existence of at least 2 separate clinical entities, *i. e.*, (1) exophthalmic goiter and (2) nodular toxic goiter. This dualistic conception in the United States has been supported by Plummer and Boothby. A number of other authorities, notable among which is von Bergmann, who support the unitarian conception, believe that the varied manifestations of thyroid disease are but different reactions by the patient to the same basic pathological process.

**Preoperative Care**—In no branch of surgery is preoperative care of more importance than it is in the operation of the thyroid gland. The preoperative preparation consists in preparing the patient to withstand the shock of technical intervention. When the metabolism is normal the question of ability to withstand a certain amount of tissue injury, loss of blood and fluid plus the shock of anesthesia must be considered. With these factors kept under control there is slight surgical risk. When the metabolism of the body is markedly altered, however, as is always the case

with toxic goiter, the effect of a simple trauma is enhanced many times.

Preoperative care must be directed to lowering the metabolic requirement of the patient as much as possible and at the same time the restoration toward the normal level of those physiological and chemical functions that have been grossly disturbed by the disease. This treatment may be divided roughly into 3 parts, *i. e.*, **rest**, use of **iodine**, and **diet**.

**Rest in bed** is absolutely essential. This is necessary not only because of the marked decrease in caloric requirement, but furthermore because of the particular features of muscle metabolism in patients with toxic goiter. Fatigue is one of the most important symptoms of the toxic thyroid patient. It is not uncommon to find definite changes in the muscles in advanced toxic goiter. Atrophy with replacement by fat have been seen by Womack in the muscles of the neck. The increase in blood flow after muscular work is much greater in thyrotoxic patients than in normal healthy persons, as proven by Means.<sup>4</sup>

In addition to physical rest, **mental relaxation** is likewise important. **Psychotherapy** plays a large part in the medical care of the thyroid patient. It is necessary that the patient be in a cheerful room and the petty comforts and whims must be catered to. Visiting friends must be selected with caution and their visits should be exceedingly short. **Occupational therapy** plays a rôle of importance. Never should detailed discussions of the patient's condition be held within hearing distance. When emotional tranquility has been established the surgeon casually may tell the patient that sometime he intends to remove the thyroid gland; the exact date, however, is not given. The majority of patients would rather not

know the exact date on which they are to be operated on. Womack calls attention to the importance of regarding the emotional reactions of such a patient in terms of epinephrine response. Nothing is more detrimental to the welfare of these patients with toxic thyroid disease than the use of epinephrine either by the physician or spontaneously on the part of the patient. Patients entering the operating room in a highly emotional state become serious operative risks.

The **barbiturates** are ordinarily the most satisfactory sedatives and recently Daniels<sup>5</sup> has characterized the action of the barbiturates as antagonistic to the effect of thyroxin on the midbrain. For patients sensitive to **phenobarbital**, **chloral** and **bromide mixtures** may be used.

**Iodine**—The use of iodine as a factor of safety to surgery of the thyroid gland is of fundamental importance. Soon after the use of iodine has been started, a striking change appears in the patient. The pulse rate slows down, the nervousness and apprehension diminish and there is a gain in weight and improvement in the well-being. The basal metabolic rate begins to fall and the thyroid gland becomes less vascular and firm to palpation. About the end of the first week this improvement, while rapid at first, begins to level off and by the end of the second week it has reached its optimum. Following 1 or 2 weeks, during which the patient's progress seems to remain more or less stationary, there appears a slow return to the original level, although this is generally not quite attained. Each case should be studied individually and its progress carefully watched. Some authorities believe that this apparent lessening of the effect of iodine is due to refractoriness to iodine on the patient's part. Means,

however, doubts this and has cited the effect of withdrawal of iodine at such a time, which is definitely associated with the more rapid return to the thyrotoxic state. Until more is known about the mode of action of iodine, this question cannot be definitely decided. With rare exceptions, however, the patient with a disturbance of the thyroid gland stands operation better before this delayed return of symptoms occurs. No great benefit has been found in changing the method of administration of iodine, namely 10 minims (0.6 cc) of iodine U. S. P. 3 times a day. While iodine in the form of compound solution of iodine U. S. P. is not markedly superior to potassium iodide or any other available iodine salt, it is easily obtainable and easily administered.

**Diet**—A nutritional problem exists in every patient with a toxic thyroid. The more toxic the case, the more important the nutritional aspect. Tissue breakdown exceeds the ability of the body to rebuild. The lower the patient's reserve the greater is the operative risk. The caloric requirements of these patients is several times that of a normal individual. The depleted reserve of the body must be replenished and the carbohydrate requirement of the thyrotoxic patient is excessive. This is due partly to greatly increased consumption resulting from increased metabolic demand and partly to loss of glycogen as a result of the adrenalin effect. Often carbohydrate depletion may be demonstrated in the liver and it is probable that there is furthermore a depletion in the skeletal muscle and cardiac muscle. Because of this, the patient's diet must contain a considerable amount of carbohydrate in a readily assimilable form.

A considerable increase in the nitrogen output in the urine of the patient always indicates protein breakdown.

With this there is muscular wasting and loss of weight. There is marked disturbance of the creatine metabolism.

Because of the specific dynamic action of protein, certain authorities believe that protein should be given sparingly in the diet. However, since in this particular instance no difference exists between the patient and the normal person, it seems that the bad effect that may ensue from the slight elevation in the metabolic rate caused by administration of protein is more than offset by the good effects of protein on the patient. There appears to be a definite association between the protein metabolism and the ability of the body to store glycogen in the liver.

**Vitamin A** reserves are markedly depleted in thyrotoxicosis and it has been suggested by some observers that there is a direct antagonism between the action of vitamin A and thyroid secretion. This latter statement, however, Wegelin<sup>6</sup> questions.

The **vitamin B** requirement of the body is dependent to a large extent on the metabolic level. With the metabolic rate markedly increased the ordinary balanced diet is not sufficient in vitamin B to take care of body needs. Most of these patients suffering from long-standing thyrotoxicosis have a deficiency as far as the vitamin B complex goes. The increased vitamin B requirement as shown by Cowgill and colleagues<sup>7</sup> is due directly to the result of an exaggerated metabolic level and the excessive utilization of more carbohydrate. These patients require enormous amounts of the entire B complex in addition to their regular balanced diet.

**Vitamin C** in cases of toxic goiter plays a less important rôle. It is true that many patients who have thyroid disease show a low level of vitamin C in the blood, but this, as available evi-

dence shows, is due to the association of this factor with the general nutritional level. It is important that adequate vitamin C be present for prompt wound healing.

**Vitamin D** is not a great factor in thyroid disease. With the marked loss of calcium in both the urine and feces in long-standing thyrotoxicosis it is hoped that this could be corrected by large quantities of vitamin D. No one has proven, however, that this loss of calcium is in any way concerned with the metabolism of vitamin D.

Concerning other vitamins, not sufficient data is at hand to permit any definite opinion to be formulated.

**Postoperative Care**—The postoperative care of the toxic thyroid patient depends on the condition of the patient at the time of the operation and the nature of the operation performed. With surgical intervention at the optimum time and the proper amount of tissue removed with minimum trauma, little trouble should be expected. There is always a marked increase in the pulse rate following operation as compared to that in other conditions. With this there is an associated increase in the metabolic rate. Water balance, therefore, is an important problem.

*Mucus* accumulating in the throat should be removed by **steam inhalation** and by medication with drugs of the **opium group**, if necessary. At all times the patient must be kept comfortable. When the environmental temperature is elevated, the use of a **cooled oxygen tent** is frequently most gratifying. If such a tent is used, however, the patient should be informed about it several days before operation, in order to prevent the terror known by many on awakening from an anesthetic in an oxygen tent.

**Fluids** may be given either subcutaneously or intravenously. The ma-

jority of patients need at least 4 or 5 quarts (liters) during the first few hours. These may be in the form of **physiologic saline solution** or intravenously as **dextrose** in either water or normal saline solution. The use of dextrose over 5 per cent when given intravenously tends to promote a certain degree of dehydration and should be used only when the carbohydrate need is pronounced. **Sodium iodide** may be introduced in the intravenous solution when this is given immediately after operation. As soon as possible the patient should be encouraged to drink **highly sweetened fruit juices**. **Cold drinks** and **ice cream** are gratefully received. When there is a marked *increase in the pulse rate*, **cold applications over the head** and an **ice bag over the chest**, as well as **cold applications to the extremities**, are of definite usefulness.

When a *postoperative storm*, or *crisis*, develops, evidence of its occurrence may be expected within from 4 to 18 hours after operation. It usually begins as an exaggerated postoperative response with a marked increase in the pulse rate. The patient is apprehensive and may become delirious. Vomiting and diarrhea are common.

The therapy indicated is that for lowering the rate of oxygen consumption in the body and at the same time lowering the emotional reaction of the patient. The use of **barbiturates** or **morphine** or **avertin** with **amylene hydrate** per rectum is justifiable.

*Delirium*, *excessive fear* and *threshing about in bed* by the patient should be controlled at all costs. As the utilization of fluids and sugar is multiplied many times, it must be compensated for by **constant intravenous drip**. Lowering of the body temperature is of real help in lowering the metabolic rate.

Frequently a *blood transfusion* is life saving. This may be administered through a cannula in place for intravenous sugar medication.

Adequate oxygenation of the patient is exceedingly important. As soon as respiratory difficulty appears it should be corrected. *Cyanosis* is one of the danger signals in a thyrotoxic patient after operation. In the absence of tracheal obstruction, this cyanosis should be treated by the immediate use of an *oxygen tent*. Great care must be exercised in ruling out the possibility of *hemorrhage* beneath the muscles as a cause of cyanosis. When this is present, the wound should be opened at once and the *hemorrhage controlled*.

Soon after the first week the patient should be well enough to sit up in a chair. Womack advises the continued postoperative administration of *compound solution of iodine U.S.P.* in the same doses as were given preoperatively until a week or 2 after the thyroid has been removed and the metabolism of the patient becomes stable. Following this, the use of iodine may be discontinued. If there are no evidences of overfunction of the thyroid and the basal metabolism is within normal range, then the use of iodine may be permanently discontinued.

Following the patient's discharge from the hospital adequate *rest* must be given until recuperation of the physical and emotional deficiencies that were present before the operation have cleared up. The usual *dietary measures* must be continued and the patient should be cautioned against too energetic exercises.

*Roentgen treatment* has been advocated for those patients in which a mild degree of thyrotoxicosis persists following operation.

**Anesthesia in Thyroidectomy**—In general, the selection of the anesthesia to be used is relatively unimportant, according to Cole and Brunner,<sup>8</sup> in the operation for subtotal thyroidectomy. Of extreme importance, however, is the skill of the anesthetist and his understanding of the physiological principles underlying the procedure. In no other condition is greater judgment regarding the operability of the patient, the time for the operation, and the extent of the operation of more importance than in thyroid surgery. Ordinarily, the surgeon and the anesthetist have their particular choice of anesthetic which they use routinely. The anesthetist, however, should have a complete understanding of all of the recommended anesthetic drugs available so that when 1 fails, another immediately may be available.

The selection of a routine in anesthesia which diminishes the undesirable features of the condition, such as hyperexcitability, increased metabolic rate, strain on the heart, etc., is of fundamental importance to the patient. Likewise, it must be kept in mind, however, that with a toxic thyroid condition there is an increased oxygen consumption, making it most necessary that asphyxia should be avoided at all events during the period of anesthesia. It is well-known that *anoxia* incident to asphyxia is apt to increase the heart rate and, therefore, cause a severe strain on the cardiac reserve and increase the blood-pressure. Anoxia causes congestion and increases the susceptibility to bleeding.

A great deal will be accomplished for lowering the mortality rate in thyroid surgery if the anesthetist keeps in mind the necessity for eliminating the *psychic trauma* as well as the avoidance of pain on the part of the patient. Much of the psychic trauma can be reduced to a minimum by dating the time of opera-

tion. Crile was the first to emphasize the importance of conferring with the relatives rather than the patient concerning the operation. Experienced surgeons favor the practice of inducing sleep in a patient's own bed before transport to the operating room.

When gaseous anesthetic drugs, such as *nitrous oxide*, *ethylene*, or *cyclopropane* are selected, the patient should be held in the lower border of the first plane of the third stage, which is the lightest degree of anesthesia that will eliminate nausea and vomiting and still permit insertion of a pharyngeal airway. When this plane of narcosis has been achieved, Cole and Brunner<sup>8</sup> insert the curved pharyngeal airway regardless of the presence or absence of obstruction. This insures free passage of the respiratory wave. If absolute quiet is achieved during the induction period, the period of excitement may be entirely eliminated, a highly desirable condition, since it is so essential that the energy of the thyroid patient be conserved to the utmost.

With the use of *carbon dioxide*, according to the Waters technic, quiet, even respirations are the rule, thus preserving much needed energy.

*Explosions* must be borne in mind constantly if highly inflammable drugs such as *ethylene* or *cyclopropane* are used. It is obvious that the open flame, electric light, switches, motors, and similar spark-producing factors should be kept out of the operating environment. To avoid sparks from metal objects in the operative field it is essential that no loose connections be permitted, particularly within the conduction system. In recent years static sparks have caused practically all explosions reported. Even greater in importance in preventing the static spark is the maintenance of a humidity of 55 or 60 per cent in the

operation field. Thoroughly moistening the mask and rubber conduction system is also important. Waters maintains that grounding of the apparatus, floors, etc., will not diminish the hazard of explosions, but may increase it. To reduce this hazard, Lahey has recommended an intercoupling mechanism which will equalize the electrical charge of the table and the gas machine in the hope that it tends to minimize explosion.

Since there is no ideal anesthetic drug yet available, a preparation must be selected which most satisfactorily meets the following requirements: (1) Minimize psychic trauma; (2) depress the basal metabolic rate; (3) rapid induction; (4) minimum effect on blood-pressure level and heart rate; (5) the avoidance of anoxia; (6) minimum laryngeal spasm; (7) to maintain quiet respiration; (8) low toxicity; (9) a wide margin of safety; and (10) to conserve the patient's energy.

**Premedication** — Premedication drugs are of great value in the production of a smooth anesthetic. The purpose of premedication is to lower the metabolic rate and to abolish psychic trauma. *Morphine* is probably the most valuable of the preanesthetic drugs since it acts directly as a metabolic depressant and indirectly minimizes emotional excitement. *Atropine* likewise is helpful because of its inhibiting effect on mucous secretion; on the other hand, atropine stimulates metabolic activity. It is losing favor, therefore, as a preoperative drug in thyroid surgery. *Scopolamine* inhibits mucous secretion similar to atropine and although scopolamine is a metabolic stimulant, its action is largely neutralized by reducing emotional excitement. On this account, *morphine* and *scopolamine* are recommended in the dosage ratio of 1:25. It must be kept in mind that if the dosage of sco-

polamine is too large, *restlessness* and even *delirium* may develop, for which an additional small amount of *morphine* or *apomorphine*  $\frac{1}{64}$  grain (1 mg.) has proven helpful.

Scopolamine is to be avoided in elderly, debilitated, hyperthyroid patients.

Other drugs recommended for premedication are *pentobarbital sodium*,  $1\frac{1}{2}$  grains (0.1 Gm.), or *phenobarbital*,  $1\frac{1}{2}$  grains (0.1 Gm.), given the evening before operation, and a hypodermic of  $\frac{1}{4}$  grain (0.016 Gm.) *morphine* with  $\frac{1}{150}$  grain (0.04 mg.) of *scopolamine* an hour before operation the following day. The use of  $1\frac{1}{2}$  grains (0.1 Gm.) of *pentobarbital* 90 minutes before the operation may be helpful in diminishing apprehension and excitement and to permit the patient better anesthesia. Sise recommends 3 grains (0.2 Gm.) *sodium pentobarbital* by mouth  $1\frac{1}{2}$  hours preceding operation and this is followed by a hypodermic of  $\frac{1}{8}$  grain (0.008 Gm.) of *morphine* and  $\frac{1}{150}$  grain (0.04 mg.) *scopolamine* 45 minutes preceding *cyclopropane* anesthesia.

The basal anesthetic agent most commonly used preceding general anesthesia may be *avertin*, *paraldehyde*, or *sodium amytal*. *Avertin*, however, is for the present enjoying the greatest popularity. Since *paraldehyde* has but slight depressant effect on respiration and circulation and has a general margin of safety, Marston has used it to precede *nitrous oxide* anesthesia in the dosage of 1 dram (4 Gm.), rectally for each 14 pounds of body weight 45 minutes before operation. On the other hand, Crile and Adams have reported a high incidence of pneumonia following the use of paraldehyde. Since paraldehyde is eliminated through the respiratory system, this complication readily may be understood. Sodium amytal is

rarely used as a basal anesthetic since its toxicity is greater than avertin when given in greater doses to produce unconsciousness.

**Complications**—Innumerable *anesthetic complications* may appear during thyroid surgery. Many of these, however, are the fault of the surgeon and not due to improper anesthesia. The most common of these is obstruction. It is rarely severe enough, however, to cause alarm. It is a most undesirable condition because of the deleterious effect on the heart muscle and the tendency to increase hemorrhage and elevate blood-pressure, due to anoxemia. In the majority of instances, obstruction will be of pharyngeal origin and can be corrected readily by adjusting the jaw and insertion of an airway.

*Laryngeal and tracheal spasm* not infrequently cause obstruction. This complication may appear with practically any of the inhalant anesthetics. It is reflex in origin and is caused by numerous factors, as outlined by Cole, including too light anesthesia, starting the operation before proper anesthetic depth is obtained, certain types of operative manipulations, especially about the superior pole of the gland, and too rapid an increase in concentration of the anesthetic agent. If these factors are kept in mind a spasm may be corrected readily, particularly if the surgeon stops operating long enough to relieve all possible sources of pressure and tension. Rarely will tracheal intubation become necessary.

*Cord paralysis* is a much more serious cause of airway obstruction and this is ordinarily caused by operative trauma. Paralysis of 1 cord only will cause a variable degree of obstruction, depending on whether or not spasm develops in the unaffected cord. When both cords are involved the obstruction may become



so severe that tracheotomy may be necessary even before the operation is finished. When the obstruction is caused by pressure from a clamp, removal will eliminate the difficulty. Ordinarily, it is difficult to determine at once whether the obstruction is caused by a spasm of the larynx or paralysis of the cords. When in doubt, *intubation* is usually the procedure of choice. At the time the tracheal tube is removed, the surgeon should be on hand and ready to perform a *tracheotomy* if the airway cannot be re-established because of cord paralysis.

*Rough handling of the gland*, particularly in the presence of a large adenoma behind the trachea, may cause obstruction. Obviously, due care in operative technic will eliminate this cause of obstruction.

Before operation, all patients should be queried concerning the possible presence of *obstructive symptoms* caused by gland pressure and an x-ray film should be made to determine the location of the trachea in the presence of a significant history of obstructions. It ordinarily is preferable to *intubate* the patient after the anesthesia is started but preceding surgical activity.

*Cyclopropane* is valuable in producing an anesthesia of sufficient depth for this procedure. *Helium* has been recommended by Sise and Lahey for minimizing the mechanical factor of obstruction. Ordinarily, the drop in blood-pressure following hemorrhage is tolerated poorly by the average thyrotoxicosis patient. When *bleeding* has been *severe*, measures, such as *transfusion* or *intravenous glucose*, should be promptly used to increase the blood-pressure.

*Pneumonia* is a rare complication in the hands of an experienced surgeon and anesthetist.

**Surgery in Thyroid and Cardiac Disease**—According to Pemberton and Miller,<sup>9</sup> a certain degree of cardiovascular disturbance is almost invariably associated with thyrotoxicosis. In such cases the clinical signs related to the cardiovascular system are easily explicable on the basis of an increased circulatory rate. The latter is merely the result of the changes in the body economy dictated by an increased metabolic rate. The most common disorder of cardiac rhythm is *auricular fibrillation*. Its *persistence* following thyroidectomy is suggestive of the presence of associated primary cardiac disease, residual cardiac injury from protracted hyperthyroidism or recurrent hyperthyroidism of exophthalmic goiter. It is important that such patients have *ample rest before operation*. When compensation is attained, the patient should be *ambulatory in a limited fashion* for several days. Debilitation from prolonged rest and the ravages of hyperthyroidism make him susceptible to postoperative pulmonary complications. This procedure gives valuable information in that this period of limited activity also affords a test of cardiac reserve. The most frequent accompanying cardiac disorders are *coronary sclerosis* and *coronary* and *hypertensive cardiac disease*. Cardiac disease as a complication accounts for approximately *81 per cent* of the total mortality. In severe cases with advanced cardiac involvement the surgeon must remember that although the chances of recovery are slim, his estimate of risk is subject to error and that every patient should be given the opportunity to avoid the status of a *cardiac cripple*.

In the opinion of the authors, the relation of *hepatic failure* to surgical risk in cases of hyperthyroidism has not received sufficient consideration. The

choice of the *anesthetic agent* to be used is a prime consideration. *Local infiltration supplemented by inhalation of nitrous oxide and oxygen* has proved effective in their experience. *Prolonged anesthesia by inhalation is avoided* and the susceptibility to *pulmonary complications is reduced*. Local anesthesia, unsupplemented, should be used for patients with obstructive dyspnea. Patients in an extremely toxic condition with limited reserve and patients with congestive heart-failure may have to be subjected to *lobectomy* to minimize the hazard. Such patients need special preoperative and postoperative preparation. Such care is most effectively achieved by the internist and the surgeon *as a team*. Finally, it should be appreciated that although the risk of operation for such individuals is great, the large number of excellent results justifies such operative intervention in selected cases.

**Surgical End-results**—Very favorable end-results (84.4 per cent) following operations for thyrotoxicosis are reported by Poate and Wyndham.<sup>10</sup> The clinical material upon which this report was based consisted of 413 patients observed from 1925 to 1937. Only 317 were available for follow-up examination 2 to 14 years after operation. *Complete freedom* from symptoms was obtained in 220 (69.4 per cent), *mild symptoms* were present in 48 (15 per cent) and *unsatisfactory results* in 49 (15.4 per cent).

Like surgeons in this country and elsewhere, they note that treatment and careful attention should not cease on discharge from the hospital. It is necessary to watch and advise each patient for about 2 years during the stage of readjustment. *Close co-operation between physician and surgeon* is not only of benefit to both, but is a necessity to the

patient. Patients with mild symptoms are capable of doing a normal day's work. Their complaints may be due to 1 of the following: Residual thyrotoxicosis, hypothyroidism, hypoparathyroidism, diminished cardiac efficiency, neurasthenia, or causes not associated with the original illness. With careful after-treatment, many of these patients will be included in the group of perfect cures.

The group with unsatisfactory results includes 13 patients who died within a few days of operation, 6 patients who died after leaving the hospital, and 30 who are still living but who cannot lead a normal life. Observations on 34 patients with auricular fibrillation convinced the authors that fibrillation depends more on the heart than on the thyroid gland. In 59 per cent of such cases normal rhythm was restored. This very favorable improvement of the secondary cardiac condition bespeaks surgical intervention rather than prolonged medical treatment. These figures also cause one to wonder if early surgery had been performed in all the reported cases, whether or not the number of cases which had re-establishment of normal rhythm might not have been much higher.

### Malignant Thyroids

**Surgical Findings**—The dividing line between benign and malignant tumors is nowhere less sharply drawn than in tumors of thyroid tissue showing papillary design. Fifteen cases of tumors of aberrant thyroid tissue found in the pathologic material of 4274 operations are presented in detail by Ward.<sup>11</sup> There were 95 malignant tumors in normally situated thyroids. Twelve of the growths of the aberrant thyroid were tentatively considered by the author as malignant and 3 as benign. From a path-

ological study of the tumors it was revealed that of 3 patients dead of lateral tumors, 2 had growths of the papillary type and 1 a malignant adenoma. Of the 12 malignant tumors, 7 were either predominantly papillary or showed some characteristics of that growth, while 5 showed no tendency toward papilliferous change. The tumors were single in only 3 instances. The remaining 12 cases were instances of *multiple tumors*, 42 located in the left side of the neck and 29 in the right. Regional or distant metastases were considered gross evidence of malignant change. It should be remembered that many of the changes which would bespeak a malignant condition in other organs are seen in the thyroid as a response to stimulation of the gland to greater activity. There is little evidence that the change from a benign to a malignant tumor of papillary structure is not a reversible process.

Ward points out that the statistical comparison of malignant tumors of lateral aberrant thyroid tissue with those arising in the thyroid proper shows that the former are found in a *younger age group*, that they are more equally distributed between the sexes and that the mortality rate is *less than one-half as great*. Despite the more favorable mor-

tality rate, the ratio of recurrence is high. Only 4 of his 15 patients have remained free from the disease after a single operative removal. Statistically, there were 2 deaths from papillary tumors, 1 from pulmonary metastases and 1 the author believes was caused by metastases from a lateral nonpapillary tumor.

Ward concluded that a guarded prognosis should be given in similar cases and that more deaths will be found in the cases reported by other investigators if a sufficiently long period of observation is maintained.

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## WAR SURGERY

By V. W. MURRAY WRIGHT, M.D.

### Fundamentals of War Surgery

Surgeons interested in war surgery will be interested in the problems presented by extensive war injuries of the extremities with lacerations or contusions of the muscles and vessels, with fractured bones and open articulations; by crushed extremities that are cold and

inert; by the wounded with multiple lesions, and by those who are in shock and almost moribund. War surgery requires a special organization: (1) Advanced surgical posts, (2) centers of treatment that are subdivided according to specialties, (3) research centers charged with the study of the biology,

pathologic anatomy and treatment of war wounds, and (4) a service of surgical information

Jeanneney,<sup>1</sup> in giving a general review of war surgery, relates his basic ideas acquired during the Spanish war, that the *latent time before deep infection* of the war wound permits a *prophylactic excision* and, if necessary, a *suture* of the wound; the penetrating wounds of the cranium permit preoperative transportation; *penetrating chest wounds, severe hemorrhage and shock do not permit transportation*; the penetrating abdominal wound should be given priority in treatment.

Jeanneney stresses the following points: (1) Lavage of the injuries only at the beginning, in order to remove the septic débris; (2) surgical cleansing of the wound, removal of foreign bodies and flattening of sinuous depressions; (3) antitetanic and antigangrenous therapy; (4) infrequent changing of dressings, even if the wound smells bad or changing only the cotton, leaving the wound itself untouched, thus avoiding unnecessary pain for the wounded; (5) supervising carefully the temperature and the general condition; and (6) giving special attention to immobilization in a good position. Immobilization by a *plaster-of-Paris cast* is recommended not only for fractures but also for wounds of the soft parts. The wounds are padded with *petrolatum compresses* and the dressings are changed at the end of two weeks.

Although closed plaster casts were used for compound fractures during the Spanish war, the author considers that this procedure should be used with prudence, because it involves the danger of "enclosing the wolf in the sheepfold." The *pain of the amputation stump* has been known to respond to daily *injections of vitamin B*. When a correctly

vaccinated subject sustains a tetanigenic injury he should be given an injection of *tetanic toxoid* so as to augment the immunity without exposing him to possible complications from serum. If doubt exists as to whether a wounded person has been vaccinated or, if the wounds are multiple and have caused severe hemorrhages, it is best to combine the injection of *toxoid with serum* treatment. If *tetanus* is developing, *serotoxoid therapy* should be employed.

### Air Transport of War Wounded

Through the centuries of man's warfares, the transportation of injured soldiers has depended upon the facilities and racial progress of the nationals affected. With the revolution of transportation and communications in the past several decades it, therefore, is not surprising to learn that German ambulance planes have been put into operation in appreciable number on the Eastern Front. The travelling speed of the large medical planes is 143 miles per hour. Schmidt<sup>2</sup> reports that airplane transportation is superior to all other methods, because, while flying, jarring of the patient rarely causes pain and the transportation time is short. The trimotor passenger plane as an ambulance plane must be considered a lucky choice. Four removable stretcher racks in the open space in the cabin carry 8 stretchers. The racks are fastened rigidly to the wall of the plane and permit no motion in any direction, except for elasticity. Short leather straps keep the stretchers from slipping. Lying in pairs, one beside or above the other, each patient is easily reached from the central aisle, which permits of easy nursing care, attention to tourniquets, change of dressings, administering of stimulants, etc. The relatively large number of spinal injuries has made it necessary to include

rubber or glass bedpans. They are now standard ambulance equipment. Since the wounded are very susceptible to cold, the planes are equipped with cabin heat of the same type used in passenger planes.

Schmidt reports that the greatest difficulty of airplane transportation is that the ambulance plane requires suitable landing and takeoff fields and is dependent on land means of transportation. At the flying fields much time was wasted with waiting and loading after the plane had landed. Such delays are avoidable if the probable time of landing is reported in advance to those at the front.

For carrying communications in the area between the rear of the front section and temporary air stations for large planes, a small scout plane would be most adequate. Such a plane could restore broken connections in the shortest time, receive new orders, pick out the most suitable open fields in the closest proximity to the wounded. The author asserts that not a single wounded man transported by himself in a reclining position has ever suffered airsickness, notwithstanding squalls during several flights. The reason for this lies mainly in the fact of the *reclining position of the body*, the *short duration of the trip* and the *avoidance of marked turbulent air currents in the proximity of the ground up to 15,748 feet (400 meters)*. Wounded soldiers have felt very grateful for the airplane transportation. The air transport of wounded obviously can be of great value in treating various cases of war injuries where time is of great importance. Such cases are (1) early gas gangrene, (2) compound fractures of the long bones, (3) cranial injuries, and (4) latent shock. Civilian surgeons who may later be called to

military service should be prepared to utilize and appreciate this contribution of aviation in minimizing the delays of former days attending shock and infection in war wounded.

### War Plane Transport of Blood Bank

During the World War thousands of soldiers died of shock who might have been saved by transfusions which have been so highly developed in recent years. Taking advantage of this increased knowledge, the medical service of the French Army have developed large blood banks in the civilian rear of the army and then devised a rapid air-borne, mobile, blood-bank dispatch to field hospitals where wounded soldiers with shock had already been typed<sup>3</sup>. Thus, transportation by air plays an important part in the treatment of military shock. The French had a fleet of aircraft to carry blood from the depots in which it is stored to the hospitals. A wire crate containing 10 bottles of blood is the unit for dispatch. To each bottle is attached a tin box containing the sterilized equipment necessary for giving the blood. There are insulated boxes for the airplanes, each of which holds 2 crates and when loaded weighs about 100 pounds. The boxes are kept loaded in the refrigerator until just before dispatch. Thereupon a block of ice contained in a tin box is slipped into the lid of the box. This, in conjunction with the kapok insulating material with which the walls of the box are lined, ensures that the temperature inside the box will not rise more than 5° C. in 8 hours. Little structural change is required in the aircraft used for the work. The boxes are merely strapped to the fuselage to prevent rolling when in flight. The type of aircraft used can carry 5 boxes of blood, *i. e.*, 100 pints.

Future development of this method can also prove useful to the Red Cross Service during civilian catastrophies, etc.

### Chest Wounds

**Treatment**—Increasing reports from Europe testify to the seriousness of war wounds of the chest. Naegeli<sup>4</sup> points out that the prognosis in cases of bilateral pneumothorax is grave. In unilateral open thoracic wounds a displacement of the mediastinum toward the uninjured side occurs with decreased ventilation of the uninjured lung and unsatisfactory blood arterialization as a consequence. *Closing of the thoracic wound* with airtight dressing or suturing soft parts improves the patient's condition, as the injurious variations in pressure during breathing become thereby eliminated. Some of the consequences of *valvular and tension pneumothorax* are tympanites over the lungs, widening of the intercostal spaces, cyanosis and dyspnea. Such cases should be treated by *puncture*, preferably with a cannula provided with a valve toward the outside. Severe phenomena of *displacement due to hemorrhage* following injury of a lung vessel also require *puncture*. A small *blood transfusion* favors arrest of the hemorrhage. *Mediastinal emphysema* requires an *incision* into the suprasternal fossa. In *pleural empyemas*, *puncturing* and *suction* should be used. Change of dressing should be done without letting air into the empyema cavity which complicates and prolongs the treatment of such cases. In view of possible *infection*, large and particularly *torn soft ounds of the thoracic wall* should be *excised* and eventually sutured. The patients may be transported best in a sitting position leaning on the injured side. Severely wounded patients or patients who have

been operated on should not be transported for 20 days at least.

With increasing reports reaching the medical literature on modern war chest surgery, it is interesting to note the results obtained in the World War by an English surgeon and his conclusions about this type of surgery in the present European War. Ryle<sup>5</sup> reviews the records of penetrating wounds of the chest admitted under his care during 1917 at a casualty clearing station near Ypres. The patients totaled 130, and 30 (23 per cent) of them died. Since none were discharged to the base until shock, sepsis and hemorrhage were under control and they were judged fit for the long train journey, it is unlikely that there was a high toll of subsequent deaths. He states that if a patient is admitted in bad condition not attributable to other wounds, the cause may be 1 of the 3 following: 1. A "leaking" or "sucking" *hemothorax or pneumothorax*, calling for immediate *plugging with wet eusol gauze and a firm pad with strapping or a binder*. (2) A *tension pneumothorax* calling for relief with the *needle*. The author never saw this as a complication of a penetrating wound; it is more likely to follow a crush injury. (3) Penetration of the diaphragm by a fragment passing through the chest and lung with damage to 1 or more of the abdominal viscera. A "leaking" hemothorax usually shows a large entry or exit wound from which there is a considerable flow or trickle or rhythmic spouting of blood or bloody fluid. An audibly "sucking" or "open" pneumothorax explains itself and calls for similar immediate treatment. The further immediate treatment in all such cases is the usual treatment for shock or hemorrhage. The procedure in *closed hemothorax*, apart from *appropriate nursing, postural measures and relief of*

*dyspnea and pain*, was to wait until the second day and then to *needle and withdraw a syringe-ful of blood*. This should be examined by staining a smear for organisms and culturally

According to the patient's condition and temperature chart, subsequent needlings for inspection and culture are carried out on the third or fourth and, if necessary, on subsequent days. In patients with the graver "*leaking*" or "*sucking*" wounds of the chest who survive the first day or 2 *surgical intervention* will nearly always become necessary for purposes of drainage of an infected effusion, toilet of the wounds and comminuted ribs and, when feasible, *removal of the foreign body*. The time for such action must be determined by the conditions obtaining in each case. Ryle has no doubt that with earlier admissions and better treatment of hemorrhage and shock, early intervention will be undertaken more often than it was in 1917 and that the primary operations with removal of fragments, repair and closure will become more usual and save lives

**Artificial Pneumothorax**—Thoracic surgery in civilian life is largely concerned with slowly progressive conditions and the operations performed are usually of election. Though industrial, auto accidents and assault cases produce emergency or complicated cases for the thoracic surgeon, these are in the minority. In war surgery, however, the situation is reversed and most of chest wound cases fall in the complicated group

According to Kretzschmar,<sup>6</sup> the treatment of chest wounds by *artificial pneumothorax* was introduced into the Italian army in 1916 by Morelli. During the Spanish War the author saw death from intrathoracic hemorrhage after a comparatively small chest wound.

Hemorrhage is intensified or prolonged by the negative pressure in the pleural cavity. The hemothorax does not check the hemorrhage, for *if the wound is in the upper part of the lung the hemothorax does not reach the level of the wound*. It should be remembered that spontaneous cessation of pulmonary hemorrhage is more probably due to the pneumothorax which usually accompanies penetrating wounds of the chest. A traumatic pneumothorax is not an indication for operation unless it is valvular or complicated by an infected effusion or by progressive hemorrhage from the lung. When there is progressive pulmonary hemorrhage and when there are foreign bodies in the lung, a complete artificial pneumothorax should be induced to cause collapse of the lung. The hemothorax, if large, should be cleared out by thoracocentesis as completely as possible, because its absorption takes a long time, causes thickening of the diaphragm and pleural adhesions, and *impedes the cardiac action* and the expansion of the sound lung, and there is a risk of pyopneumohemothorax with a doubtful prognosis

Artificial pneumothorax has its therapeutic effect on the wound of the lung. It stops or reduces the hemorrhage from the lung, prevents the obliteration of the sinuses and the formation of adhesions between the visceral and parietal pleura, protects the lung from further damage due to movement of foreign bodies and prevents inflammation of the lung caused by these foreign bodies. Consequently, artificial pneumothorax should have a permanent place in the treatment of wounds of the chest, whether in military or civilian practice

### War Wounds of Extremities

**Treatment**—Cohen and Schulenburg<sup>7</sup> report observations on 266 cases

of gunshot wounds of the extremities. The smallness of a wound of entry is not always an indication of the degree of resultant internal damage. Since even small bomb splinters were often found to have produced severe internal destruction of the tissues, consequently the authors always employed *general anesthesia*. The routine use of *evipal* and *pentothal sodium* followed by *gas and oxygen* was most satisfactory. In contrast to former methods of surgery, it is to be noted that with the exception of excision of the skin edge, no extensive débridement was carried out, but the wound was laid widely open by means of several radiating incisions. No attempt was made to excise or trim muscles. In packing, care was taken that there should be uninterrupted drainage from the cellular spaces between the muscle bellies. It may surprise many surgeons to learn that tendons were not immediately sutured, but their frayed ends were removed and bone fragments were removed only when completely detached. No early suturing or trimming of divided nerves was done. The operation was always preceded by x-ray examination. Foreign bodies were removed *only* when readily accessible. Large splinters were always removed but not the small ones lying some distance from the entry wound. In a few cases, localized abscess formation around a foreign body subsequently necessitated incision. Petrolatum gauze was used for packing. A thin layer of sterilized plaster wool was placed over the wound; *the rest of the plaster was skin tight*. Altogether 84 cases due to gunshot wounds were treated in plaster. Of these, 54 cases were compound fractures, 36 being of the upper extremity and 18 of the lower. Following the method adopted by surgeons in the Spanish War, all compound fractures were treated in closed plaster

casts. Reduction was obtained only by manual traction and *maintained while the plaster was being applied*. Of 207 wounds involving only the soft tissues, 30 were treated in plaster. These were extensive wounds and the same principles were applied as if an associated fracture had been present.

All patients operated on received a course of chemotherapy. An initial dose of 3 tablets of *sulfanilamide* was followed by 2 tablets every 4 hours for 48 hours, and then 1 tablet every 4 hours for 48 hours, making a total dosage of 5 drams (19.5 Gm.) in 4 days. The nursing staff was told that *no dose was to be omitted, even at night*. No toxic effects were observed from this dosage. There were no deaths and only 1 limb was amputated. The results reported by Cohen and Schulenburg are surprising as no mortality occurred in their total group of cases. The failure of severe infections to develop which would have led to generalized septicemia can only be explained by *early adequate drainage immobilization* and "*maintained*" *chemotherapy*.

### War Fractures

**Trueta Treatment**—At the Royal Society of Medicine in London, Trueta,<sup>8</sup> late director of surgery at the General Hospital of Catalunya, Barcelona, described his method of treating war fractures, which gave good results in the Spanish civil war. Advances in the treatment of compound fractures have always been secured by the experience of war. He particularly discussed injuries from aerial bombs, which were more destructive than those from bullets. No measures against infection, such as antisepsis or serum, were used without first excising damaged tissue. Contrary to the opinion held during the World War by surgeons, such as Leriche, he believed



that the greatest danger of infection lay not in bone but in muscle, which was favorable soil for anaerobic infection. This has been shown to be true in civilian life as well as in the last war by the high incidence of gas gangrene infections which spread up fascial layers and muscle planes.

In extensive wounds of the limbs, Trueta observed clinically, perhaps for the first time on a large scale, that true shock is the result of absorption of disintegrating tissues. Other European surgeons have since confirmed this earlier and important observation made by Trueta. After air raids on Barcelona he operated radically on hundreds of persons with severe wounds of the limbs within one-half hour and sometimes within 20 minutes. After treatment of the primary shock, a meticulous operation was performed, all devitalized tissue being removed. Trueta's personal description thus disposes of the erroneous opinion held by some that he did not débride, but simply encased wounds immediately and completely with plaster-of-Paris. When operation was undertaken immediately, it was common to observe that secondary shock or generalized infections did not occur.

He found that movement increased the dissemination of infection in the body and that rigorous immobilization prevented it. This could be obtained only by enclosing the limb in a rigid casing which prevented all movement but permitted good circulation. The only material which supplied this requisite was *plaster-of-Paris*. Its only disadvantage was that it prevented examination of the wound, but this he seldom found necessary. In the upper limb, if properly applied, the closed method was always satisfactory and gas gangrene and septicemia were very rare. In the lower limb, the leg and the thigh must

be separately considered. In *fractures of the leg* the circulation of the foot and the local circulation in the wounded part and the possibility of excising devitalized tissue must be estimated carefully. If, in spite of excision, there was still doubt about the vitality or the circulation, one should wait a day or 2 before putting on plaster, using open treatment with continuous traction. If amputation became necessary, it could then be performed without loss of time. In the *thigh* the indications were the same, but the local circulation of the tissues surrounding the wound was more important than the general circulation of the leg, which was easier to estimate. By this treatment many lives as well as limbs could be saved and gas gangrene disappeared from the hospital.

The treatment used by Trueta in the Spanish War has contributed greatly to naval and military surgery in simplifying transportation of the wounded, thus emptying hospital beds close to the front. Formerly, many patients could not be moved to rear hospitals because their limbs were suspended from Balkan frames and infused with continuous Dakin's solution. Trueta observed that reduction of fractures must be secured by traction on the operating table. The plaster-of-Paris should then be applied under an anesthetic directly on the skin, without interposition of raw cotton or stockinet. Only the anterior-superior iliac spine, the os calcis and the achilles tendon required to be covered with cotton. The immediate benefits of the plaster treatment were absence of pain, rapid disappearance of shock and return of appetite. In 1073 cases removal of the plaster for infection was necessary in only 0.75 per cent. The first plaster cast was retained for 6 weeks.

In a discussion of the paper, Cope described it as momentous and bidding fair

to revolutionize a most difficult war problem. One speaker called attention to the disagreeable smell due to saturation of the plaster with the discharges. Trueta replied that in a certain number of cases yeast obtained from breweries was applied and mitigated the smell. Though the technic of Trueta is vastly different from that practiced in the past by surgeons generally, his findings have since been confirmed by French and English military surgeons. If further reports from Europe continue to approve his radical form of treatment, he will have contributed greatly to the injured both in military and civilian life.

### War Injuries and Hysterical Contractures

Civilian surgeons entering military service must be prepared to recognize and cope with hysterical contractures which may be considered as subconscious malingering or the product of an escape mechanism. In this connection the report of Sir Arthur Hurst regarding hysterical contractures following war injuries is interesting.<sup>9</sup> He observed that in civil life contractures following injuries were comparatively rare but after war injuries they were frequent. During the World War the nature of these contractures was much discussed but only toward the end did it become almost universally recognized that they were hysterical and could be quickly cured by proper treatment.

The most common contracture followed injury to the soft parts of any type. Sometimes there was no wound, only a twist or a sprain. A limb was sometimes found completely stiff after amputation of a hammer-toe or removal of a semilunar cartilage, but this was amenable to psychotherapy. The postures were of great variety. The commonest developed in the hand and were

of 2 main kinds: With the fingers stiffened in extension or tightly flexed into the palm. One patient's hand was contracted for 2½ years and, when cured at a single sitting and the hand was opened, the nails had grown deeply into the palm. Fixation of the wrist was infrequent; of the elbow, frequent; of the shoulder held tightly to the side, occasional. In a number of cases the toes were affected and the patient walked on the ball of the foot. The knee and the hip were often fixed. Immediately after the injury the patient adopted the most comfortable position and this might develop into a contraction. In some cases the limb was put into a splint and after its removal maintained the same position. The limb was fixed because the patient had lost the idea of movement.

Treatment in the early days of the war consisted in a certain amount of suggestion and occasional hypnotism, but later Hurst and his colleagues found simpler methods of *psychotherapy* more valuable. The patients were not commonly hysterical and never had had "shell shock." *Persuasion, manipulation* and *re-education* were found effective and the ideal patient was cured merely by telling him what to do. It was explained to him how the contracture developed, that it was necessary to rest the limb after the injury, but that when the splint and bandage were taken away the limb should be moved. The patient was taught to relax the limb, and the physician moved the affected part a little and allowed it to relax again.

*Psychotherapy* rather than physical therapy is the treatment of choice in these conditions. According to J. B. Mennell (physical therapist), if there was 1 condition more than another with which the physical therapist should not interfere, it was these contractures. Unraveling them by force was a barbarous

method and the contractures recurred. While nothing surgical can be done for conditions of this sort, a thorough appreciation of hysterical contractures will aid surgical officers in saving valuable time and labor by routing such individuals to other departments or distant points where proper treatment can be instituted.

### War Neuroses

With America arming rapidly and with thousands of civilians being inducted into the armed services, civilian doctors who are being called to duty to treat these soldiers and sailors, in peace or in possible future warfare, ought constantly to bear in mind the condition commonly referred to as *war neurosis*.

This condition is *not a new entity* as witness the articles upon the subject written during and after the World War. It is a new subject, however, to the younger members of the profession who had no experience with the last war and to other older members whose experience perhaps has been mainly with civilians.

European army medical officers again have been confronted with this difficult problem and recently it was the subject of an investigation by the British Ministry of Pensions.<sup>10</sup> According to this source, there appeared during the last war a large number of neuroses engendered by fear, shock, exhaustion, physical and mental strain or lack of sleep, which caught the medical officers of the army unprepared with any organization or agreed method of treatment. These neuroses were popularly called "shell shock," for it was supposed that they were due to the physical effects of high explosives. But it was found that *similar symptoms occurred among men who had never been exposed to explosions* and which were also well known in civil

life. Many men who were blown up or buried beneath débris to the same extent, moreover, returned to duty *without suffering any durable effects*. It is evident, therefore, that among the human race there are 2 distinct groups of individuals: (1) Those who can take it, and (2) those who cannot. Like another recent war expression, there are the "haves" and the "have nots." The victims of "war neurosis" are those who "have not" the psychological background of facing realities and seeing things through. Like many cases of dementia precox, they are *ostriches* who bury their heads in the sand and refuse to see dangers rather than face them. These facts ever must be remembered by military and naval medical officers when "a given case allegedly diagnosed as such and such a condition fails to fit the picture even after due consultations and investigations" or when "an actual surgical or medical condition, after the best commonly prescribed form of treatment, fails to respond as other similar cases do and when *malinger*ing is suggestively present following patient investigations which have failed to unearth a cause for the bizarre result." In short, unusual conditions and unusual results will be encountered most often in *unusual patients* and these unusual patients are usually *candidates* for war neuroses.

In the latter part of 1939, the British Minister of Pensions convened a conference under the chairmanship of Lord Horder to advise the government as to the general principles for dealing with these cases. Its report has just been presented and issued to the British medical services.

The report points out that *most* of these neuroses took the form of either an anxiety state or hysteria. The anxiety state has a *common characteristic, i. e.,* the constant presence of fear or anxiety

accompanied, to a greater or lesser extent, by *vasomotor and visceral concomitants*. The source of anxiety was the fear of being found afraid or of financial loss and domestic worries. The anxiety is out of all proportion to the cause. Hysteria provides the clearest example of neurosis due to *failure of adaptation* as the result of conflict between individual needs and social requirements. *Suggestion* is the most important factor in causing the symptoms. Physical manifestations of severe emotional disturbance, such as mutism and tremors, or temporary loss of power in the limbs due to a minor physical injury, are readily *perpetuated* as hysterical symptoms in men subjected to physical or mental stress. It was noted that suggestions by medical officers, in the course of examination were often responsible for such symptoms. Consequently, physicians would do well to remember and practice that ancient Greek saying: "Beware of that erring member, the tongue." Underlying the process of suggestion is a conflict between the instinct of self preservation and the ideas of duty and self respect. The development of the symptoms satisfies the patient's ethical requirements and provides an escape from duty on the ground of physical incapacity.

These findings but support previous observations recorded by psychiatrists, that individuals of this type, though apparently normal in ordinary circumstances, will lie and mangle, *perhaps subconsciously*, to whatever extent that provides them an exit or *way out* from a mental situation which *for them* is impossible to face or continue.

Taking a lesson from mistakes encountered in treating cases of war neuroses in the World War, the British commission recorded that in 1920 the army council appointed a committee to

collate the medical experience of that war for future use. This committee reported as follows: (1) The term "*shell shock*" has been a gross and costly misnomer and *should be eliminated*. It is a catch-word which *reacts unfavorably on the patient* and others. (2) The war produced *no new nervous disorders*. The cases formed 3 classes: (a) *Genuine concussion* without visible wound as a result of shell explosion. This amounted to only *5 to 10 per cent* of all cases. (b) Emotional shock, whether acute in men with a *neuropathic disposition* or developing slowly as a result of prolonged strain and terrifying experience, the final breakdown being sometimes due to some trivial cause. This formed *80 per cent of all cases*. (c) Nervous and mental exhaustion, the result of prolonged strain and hardship.

Every surgeon who is experienced with civilian *traumatic shock* and every general practitioner who has observed many instances of *emotional shock*, following sociological disruptions in familial life, know all too well, regardless of how strong an individual may be, physically or mentally, that even the normal body and mind can stand just so much and no more. When the "no more" point is passed (that added straw on the camel's back), something "snaps" and a new, strange person presents himself. Such an individual (normal) apparently goes on a "sit-down strike" with life. He refuses to act, to listen to earnest entreaties and sound advice or even to actually be interested in his own welfare—immediate or future. Physiologically, he is resting or relaxing. Psychologically, he is getting his "*second wind*," even though he may not realize it consciously. Such normal individuals, when treated with considerate patience, and not otherwise overly treated, sooner or later manifest the rubbery or elastic

make-up of their psyche and eventually "bound back" into normal activities. They may be a little grayer and less "gay" but nevertheless they return completely to a "full, sane, economic and social life."

This final and happy result in the normally minded individual is not to be expected in the subnormally minded person who commonly is referred to as a "weak sister." This latter type of person, even when only subjected to minimal shocking episodes, has no "rubber system" which will permit him to bound back into normal activities regardless of whether he desires to do so or is "running to cover."

It should be remembered that although the experience of the British Medical Services showed that most cases of war neuroses developed without gross physical cause, up to 10 per cent were caused by concussion and another 10 per cent were due to prolonged strain, fatigue, etc., in normal individuals. They found that the diagnosis of concussion should be made only when the history or symptoms leave no doubt of physical injury by the direct explosion of a shell. The actually concussed patient becomes *immediately unconscious* or at least severely dazed. When the immediate effect passes off there is *complete amnesia* for a period *immediately before and after the injury*. Patients suffering from emotional shock may say that they became unconscious, but careful questioning will show that they can *recall most of their experiences*.

The British commission concluded that as to *treatment*, the first essential when these patients arrive at an aid post is to convince them that they have received *no serious injury*. When confusion, excitement, loss of memory and disorientation are the chief symptoms, *rest, warmth, hot drinks with plenty*

*of sugar* or a dose of *bromide* or *phenobarbital* will be necessary. *Restless or excited patients* may be given a hypodermic injection of *morphine* or soluble *phenobarbital* combined with *hyoscine*. When *hysterical symptoms* predominate, an attempt should be made to remove them by *suggestion*.

Past experience and the experience of foreign medical officers in the present war show that, naturally, all those physically injured should be given immediate treatment of the first order and that *physical shock* is to be combatted with *sedatives, saline and glucose solutions* intravenously, *posture, warmth* and *plasma* or *bank-blood transfusions* when indicated. When, however, "a given case fails to fit the picture" or when "an actual case of shock fails to respond to known appropriate treatment," and concussion, actual cerebral damage, etc., are definitely ruled out, the assumption must then be that the given case is very *probably* a so-called "*war neurosis*."

Hospital beds never ought to be occupied by individuals who do not deserve their occupancy and when such beds could be filled more deservedly with those requiring their use. Economically and administratively, "war neuroses" patients are a financial and physical loss—all because of a thin, unappreciated and gossamer cerebral spider web.

Considering the mental background of such persons, the fact that they are "running away" from "front line problems" and that they can only be relieved from their mental anxieties or fears which are concerned with "nearness to danger," it would seem that the most practical thing which naval and military medical officers, who are primarily interested in "effectives," can do immediately is to evacuate such patients, as

soon as the condition is recognized, to base hospitals and the "far, safe rear"!

Thus removed from fear, anxiety, etc., such patients readily can be made ambulatory, empty needed beds, conserve medical and nursing care, be close to psychotherapy or relatives and friends and at least serviceably and profitably perform noncombatant duties which, after all, they are only from a psychological point of view capable of being trusted to perform well.

Lastly, medical officers of the armed forces should consider, in managing the sick or injured, that racial fundamental characteristics make for many differences in the recovering from medical or surgical ills. America being the "melting-pot of races" that it is, contains citizens with very divergent mental backgrounds. As is well known, the Finn is a hardy individual, so is the Norwegian and Swede. The Scots are dour, taciturn and uncomplaining. The English and Welsh are bulldoggish and phlegmatic. Some Irishmen are tough-as-nails and some are as excitable as the French who once invaded and intermarried with them. Jews are very prone to be hysterical. Negroes, like American Indians or the Chinese, can be so stolid that they will accept the suturing of wounds without an anesthetic and without "batting an eyelid" or they can also revert to voodooish and primordial instincts and be fearful of even shadows.

With all due respect to the races and creeds of the men making up our armed forces, military and naval surgeons will undoubtedly profit much, in caring for their sick and injured, if they ever remember the teachings of the ancient Greek preceptor, Plato (429-347 B C), who said:

"The greatest mistake in the treatment of disease is that there exist physicians taking care of the body and physi-

cians taking care of the soul, as these ought not to be separated from each other . . . but just this fact is overlooked by the Greek physicians and therefore many diseases escape them, as they never see the whole"

### War Shock

**Surgery and Insulin**—Traumatic shock occurring among war injured differs from accidental shock in that the latter is sudden, unforeseen and, therefore, not complicated psychologically by prolonged periods of fear, depression, etc. According to F C Mann and his collaborators, a large number of men are found at the front with a treacherous syndrome characterized by vasomotor, circulatory and *psychic insufficiency*, the result of a series of diverse syndromes due to hemorrhage, emotion, pain and fatigue and to toxic and infectious absorption.<sup>11</sup> Shock so defined is a complication involving *depression and toxemia*. It is *frequently fatal*. Aid must be given quickly to the wounded before complications and the critical moment occur which set the vicious circle of shock in motion. Early and thorough surgical treatment of infection prevents the accumulation of toxic products for later absorption. Preventive therapy may be adapted to certain conditions such as hemorrhage, nervous exhaustion and gas poisoning. *Curative therapy* consists in restoring body temperature, maintaining the activity of the cardiovascular system by physiologic serum employed in moderation and a constant check of the venous pressure. *Acidosis* must be combatted by *sodium bicarbonate* and *anoxemia* by *oxygen*. These are purely physiological needs. Besides, certain manifestations will control therapy and make mandatory transfusions in cases of hemorrhage, of *blood stagnation* and of *complete paralytic vasodilatation*.

According to the views recently presented by G. Jeanneney and L. Justin-Besancon before the Academy of Surgery of Paris, 2 significant facts have appeared: A *tourniquet retards* the appearance of *shock*; *amputation cures it*, even if performed during complete and grave shock. The rôle of *absorption of proteins devitalised by the trauma* is thus brought out.

Lambret stressed 2 principal factors in the origin of shock: (1) An immediate neurovegetative factor whose point of departure was the wound, with multiple small filaments of the sympathetic nerve; (2) a delayed toxic factor caused by the pressure of liberated proteins in the blood. Lambret concluded that the essential remedies against shock consisted in *transfusions* in large quantities and large doses of *insulin*.

Concerning the occurrence of shock among the war injured (and this includes bombed civilians), increasing reports from Europe continue to inform us that such shock is a combination of not 1 but many different factors and that the best surgical results will be obtained in treating such cases by an appreciation of and attendance to all the etiological factors concerned.

### Wound Shock in War Surgery

**Treatment** — The Committee on Traumatic Shock and Blood Transfusion, appointed by the Medical Research Council of the British Isles, has presented a report on the treatment of wound shock.<sup>12</sup> As the Committee consists of the leading physiologists, biochemists, pathologists, physicians and surgeons of the day, the report is for the time the last word on the subject. Wound shock cases are divided into 2 groups, *i. e.*, primary and secondary, or delayed shock. *Primary shock*, which follows soon after injury and is not due

to hemorrhage, resembles fainting. It responds to simple measures. *Secondary or wound shock* develops insidiously some hours after injury. It is characterized by weakness, pallor and raised pulse rate and, in advanced cases, by lowered body temperature, sweating, low blood-pressure, rapid, thready pulse, vomiting and intense thirst. It is important that medical officers should train themselves to recognize wound shock in its earliest stages, for it is then that treatment is most likely to be effective. Wound shock closely resembles hemorrhage clinically. Shock results from many factors *besides loss of blood, i. e.*, fatigue, dehydration, pain and exposure to cold and wet—all of which demand attention in treatment. In the majority, active steps to restore blood volume must be taken as early as possible.

During military operations the most that can be done in advanced positions is to limit hemorrhage and loss of plasma by a *firm bandage* or *tourniquet* and by *splinting* to prevent pain and local loss of plasma due to movement of a fractured limb during transportation. It is of great importance to give *water freely and repeatedly* except to those who are unconscious or have abdominal wounds. It should preferably contain *1 teaspoonful of salt to the pint*. The army *transfusion* apparatus allows blood or plasma to be administered at least as far forward as main dressing stations. *Open wounds of the chest* should be *closed immediately*, as otherwise they have a high mortality.

A patient unfit by reason of shock for immediate operation should be put in a *resuscitation ward*, where greater rest and quiet can be ensured than in a busy general ward. The most valuable single method for combatting *shock* is *blood transfusion*. Whole blood is of proved

value, while human plasma or serum, because of its superior keeping qualities, is more convenient under field conditions. In extensive *burns*, in which reduction of blood volume is due entirely to loss of plasma, *replacement by plasma or serum* is theoretically correct. When blood, plasma or serum is not available, *isotonic saline or dextrose solution* may be used, but the restoration of blood volume is only transient by intravenous infusion of these solutions and is not devoid of risk. Because of the *dehydration, repeated and copious drinking of fluids* should be encouraged, with the exceptions mentioned. If necessary, the rectal route may be used. *Oxygen* should be given to all who manifest *cytosis* of the lips, ears, or nails. It is especially necessary in any interference with respiration, as in chest wounds. In cases of *infected wounds*, absorption of toxins aggravates shock. *Infected tissue* therefore must be *promptly removed* and *chemotherapy* and other forms of treatment given.

For cases requiring *anesthesia, gas and oxygen, combined with ether*, if necessary, is the mixture of choice, provided a skilled anesthetist and apparatus are available; otherwise, *ether* alone should be used. Chloroform or spinal anesthesia should not be employed. The administration of an anesthetic to shocked patients requires special care, as their circulation and the oxygen-carrying power of their blood, though having apparently been rendered near normal by transfusions, plasma, etc., are really only pseudonormal. Such patients must be regarded as operative risks, somewhat like severe alcoholics, when surgery is necessary, *i. e.*, an alcoholic is potentially subject to delirium tremens and a recently shocked case is potentially subject to further shock which on a second oc-

currence may prove more severe than the first and terminate fatally

### "Trench Foot"

As the condition termed "trench foot" rendered thousands of soldiers in the World War unfit for combat service and increased hospitalization work, army surgeons will be interested in the most recent observations from abroad regarding this entity which has recurred in European armies.<sup>18</sup> Christian Champy and Roger Goujard reported before the Academy of Sciences and the Academy of Medicine, of Paris, the rôle of vitamin B deficiency in trench foot, which has again made its appearance in the present European War. The symmetry of the lesions, the fact that only certain army units and certain classes of troops are troubled by it, its frequency in alcoholic persons and the effect of the cold season have always pointed to an internal agent, *probably vitamin B deficiency*. Unlike beriberi, trench foot is not usually accompanied by generalized neuritis. After subjecting animals to a regimen deficient in vitamin B, they were exposed to conditions similar to those of the soldiers in the trenches. Controls were used and were given the same diet but without exposure to cold. The authors found that the accidents of vitamin B deficiency appeared much earlier in animals exposed to cold. They believe that the process of thermogenesis activates a larger consumption of glucides, in the production of which, it is generally agreed, the effect of vitamin B can be recognized. The edemas of trench foot are attended by degenerative processes in the sciatic nerve, while phenomena of general neuritis are not in evidence. Their conclusion is that trench foot is preceded by a vitamin B deficiency and that the best *prophylaxis* consists in supplying regular doses of



this *vitamin*. Other measures should include the *elimination of tight-fitting equipment* and the furnishing of *water-tight shoes*.

Leriche, who has pioneered so much in peripheral vascular disease, conducted studies on trench foot at the *Centre de recherches de chirurgie vasculaire* of Lyons. He believes that trench foot is an excellent example of a functional disorder followed shortly after by a definite anatomic condition. An observation of his is that of stoppage involving the arteries. Men afflicted with trench foot are arthritic to the point that long after healing they often suffer ischemic crises and cyanosis of the feet in winter. Leriche recommends *infiltration anesthesia of the sympathetic nerve* as a systematic treatment of urgency. Stricker and Buck obtained immediate alleviation and accelerated cures by means of *lumbar infiltration*. It would seem, therefore, that the best way to combat "trench foot" is (1) *prevention* by adequate *protection of the feet* and dietary measures to insure an adequate intake of *vitamin B*; (2) when the condition has appeared, cases should be *hospitalized*, the feet encased in *extra warm socks*, *postural exercises* instituted, *suction boot treatment* given in selected cases, the *vitamin B intake increased* and *neuroanesthesia* given by the surgeon.

### War Wounds

#### Microorganisms in War Wounds

—Levaditi, having made a study of the germs found in war wounds during the period of 1914-1918, determined to compare war wound cultures in the present war with those of the World War.<sup>14</sup> He and his collaborators emphasize the frequency of anaerobic germs in war wounds. In comparison with the majority of wounds sustained in civilian

life, it is not unexpected to learn that soldiers, living and being injured on earthy terrain, would have a high incidence of anaerobic germ infections. Even if a soldier is wounded by shrapnel, bomb splinters or bullets which have not first hit and been contaminated by earth, which usually contains spore-bearing and anaerobic organisms, it must be remembered that soldiers in the open and in trenches not only have their clothes constantly soiled by earth but that due to the infrequency of baths, etc., their skin is constantly contaminated with a multitude of germs which cause no harm until there is a wound of entrance or until they are driven deep into tissues by mechanical objects.

In this connection, it very likely may turn out to be that in future years we will have conflicting reports regarding war wound infections in the naval services, in the air services and in the military services (infantry, artillery, tank corps, etc.). Such confictory reports should be anticipated in advance, as certainly sailors wounded on ships at sea or aviators wounded in ships in the air, in contrast to soldiers wounded in and on earth, would constitute 3 separate germ infection groups.

It is interesting to note the findings in 317 samples of culture from military war wounds examined by Levaditi and his collaborators in the present war. They found that their present observations differed little from those of 25 years ago. The analysis showed, however, the following:

- 7% of the wounds were sterile.
- 19% showed a single organism.
- 32% showed 3 different germs
- 19% showed 4 different germs.
- 23% showed 2, 5, or 6 different kinds of microorganisms

It is evident immediately (from this study) that the majority of war wounds

are infected with multiple forms of microorganisms and that most primarily infected wounds are multiply infected.

The species most generally observed were Staphylococci (85 per cent), Friedlaender's bacillus, Clostridium welchii, Streptococci, the Enterococcus and Bacillus pyocyaneus. The Streptococci showed an increase from 19 per cent in 1917 to 58 per cent in the present count.

These studies not only reveal the percentages of common infective organisms, but also show that the vast number of war wounds are infected by germs of the gram-positive type which McDonald, Hoogerheide and Murray Wright have demonstrated are quickly and effectively killed by a new germicide which is a solution made from the extract of soil bacteria which kill other microorganisms and which is elsewhere described.

Levaditi isolated 12 different strains of Streptococci in pure culture. They were all facultative anaerobes and generally of feeble virulence.

Though cases were treated by azo derivatives, especially p-aminophenylsulfamides, applied *in situ* and as reported upon by Perrin Long, of Johns Hopkins University, the drug had no direct effect on the germ itself. Apparently, the results obtained depend upon individual resistance.

**Prophylaxis**—To test the prophylactic value of *antitetanic serum*, von Karnitschnigg<sup>15</sup> investigated the problem of serum prophylaxis on the basis of 34,314 injuries. Tetanus antitoxin was administered to 16,269 and was omitted in the treatment of the remaining number. None of the patients who had been subjected to serum treatment developed the disease, while of the other group 29 did and among these there were 12 fatalities. This, certainly, is a graphic illustration of the use of antite-

tanic serum. Karnitschnigg also concluded that the effectiveness of excision of the edges of the wound must be rejected. It was not possible in 9 injuries (injuries from electric current and extensive excoriations), while in 1 case tetanus developed in spite of the excision. While serum prophylaxis of tetanus has certain disadvantages, such as the skin eruption with its unpleasant sequels, there can be no choice between these complications and tetanus. The greatly feared anaphylactic shock can be avoided almost entirely if the rules regarding desensitization are followed. Only 1 case of shock was observed in Karnitschnigg's series. The author concludes that serum prophylaxis of tetanus is an essential part of modern wound therapy and that he would not dispense with it under any circumstances.

**Tetanus Anatoxin versus Antitoxin**—If recent experiments in France performed on horses can be duplicated in humans exposed to tetanus infections, the incidence of tetanus in military and civilian injured will be markedly reduced. In a recent meeting of the Académie des Sciences of Paris<sup>16</sup> Gaston Ramon and Edouard Lemetayer set forth the value and duration of the immunity conferred by tetanus anatoxin (toxoid). Thousands of animals, chiefly horses, have been immunized by the anatoxin (toxoid) with 2 injections of 10 cc. at intervals of 1 month. A little tapioca powder is added to each injection to aid the immunization. A year after the 2 injections a third injection is administered, likewise of 10 cc. This study was conducted for 9 additional years. It demonstrated the importance and stability of the immunity conferred by anatoxin. In 127 control horses the antitoxin rate was equal or superior to one one-hundredth of the international unit and often reached one-third. It never

went below one three-hundredths. The immunity conferred lasted for at least 8 years. Ramon and Lemetayer found that before antitetanus vaccination was generalized, about 50 cases of tetanus were expected out of a total number of 13,000 horses. If prolonged immunity in human cases can be similarly produced, soldiers and sailors thus inoculated upon induction into service would be protected from tetanus infections for the duration.

**Treatment — Chemotherapy** — The predominant part played by hemolytic streptococci in wound infections was pointed out by Colebrook<sup>17</sup> as the most striking lesson of the war. Colebrook believes that this single bacterium was responsible for 70 per cent of all the deaths due to wound infection. Furthermore, it produced the majority of the complications such as erysipelas, cellulitis and septicemia.

Of 49 positive blood cultures in men with septic compound fractures of the femur, 44 showed a pure culture of hemolytic streptococci. Whether these organisms were carried into the wound at the time of injury or whether they found entrance during transmission from case to case is impossible to state.

Fifteen per cent of wounds were found by Stokes and Tyler to be infected by hemolytic streptococci on admission to the casualty clearing station, approximately 12 hours after the wounds were inflicted. A much larger number of wounds was found to be infected a few days after the patients were at the base hospital. One hospital gave a figure as high as 90 per cent for these infections.

Colebrook and his associates were, of course, interested in finding measures for the control of these infections. Experimental observations on mice showed that the prophylactic use of *sulfapyri-*

*dine* or *sulfanilamide* injected into mice protected the animals from infection. From this observation these authorities deduced that with a certain amount of sulfanilamide present in the circulating blood at the time the streptococci were introduced into the body, an acute infection could be prevented. If the bacteria were implanted at the time of injury, prophylaxis must be begun at the earliest possible moment. One prophylactic dose given by mouth shortly after the injury would be excreted within 10 to 20 hours. In planning preventive measures against infections that might develop in the hospital several days after injury, it was necessary therefore in order to maintain an adequate concentration in the blood during the whole period of danger, that administration must be continued for at least 4 days. By the end of the fourth day the wounded tissues would presumably be walled off and if infection did finally occur it would be much less dangerous.

The amount of drug necessary for successful prophylaxis in man is not clearly known. Fuller and James offered data suggesting the following plan of dosage designed for rapid absorption during the first few hours and slow continuous absorption thereafter: For the first dose, 23 grains (1.5 Gm.) or 3 tablets of *sulfanilamide dissolved in 1 per cent hot citric acid solution or hot lemon*; a second dose of 7½ grains (0.5 Gm.) or 1 tablet, whole or crushed, in order to delay absorption. Following these first 2 administrations, subsequent doses should be 7½ grains (0.5 Gm.), whole or crushed, at 4-hour intervals for 4 days, until a total dosage of 3½ drams (13.5 Gm.) for the 4 days was administered. It is necessary to check the blood concentration and likewise toxic effects should be noted.

When the infections are already present, the dosage is essentially similar to that used in civil practice. Some evidence warrants the suggestion that *sulfapyridine* is more effective than sulfanilamide in *gas gangrene*. To facilitate absorption, the first 3 doses of 15 grains (1 Gm.) each should be given well crushed and dissolved as completely as possible at an interval of from 1 to 3 hours.

In the first 24-hour period from 1½ to 2 drams (6 to 8 Gm.) should be given and the following day the dose may be slightly reduced if the clinical condition is improved. For infection by the hemolytic streptococcus 15 grains (1 Gm.) of sulfanilamide should be administered every fourth hour for the first 1 or 2 days and this can be reduced gradually with improvement of the patient. When infection is severe 2 drams (8 Gm.) should be administered on the first day and the drug should be continued for 4 or 5 days after the temperature has fallen to normal and the clinical condition has become satisfactory. It should not, however, be continued after that time just because there is still streptococci in the body discharges.

A leukocyte count should be made on the seventh day of treatment in every case in which large doses were administered because of the danger of granulocytopenia.

**Closed Plaster Treatment**—In the treatment of infected war wounds, Girdlestone<sup>18</sup> recommends: (1) In the débridement, the general rule is to excise, as far as practicable, infected tissues and tissues devitalized by bruising or by the impairment of circulation. (2) It is advisable to lay open rather than suture when suturing would involve tension and devitalization of the skin or deep parts. (3) There should be a varying degree of "saucerization," which

allows natural retraction of the muscles to the position of equilibrium and involves a laying open for free drainage of all pockets or areas of heavily infected or damaged tissue which cannot properly be excised. For serious destructive wounds the requirements vary from the saucer to the cup; but there are many wounds in which no such formidable exposure of the deep tissues is indicated. Nothing more may be needed than a layer of broad wick laid between the edges of the wound after débridement. (4) The plaster splintage has a *dual purpose*, i. e., (a) the restoration of function by keeping the bones, joints, and muscles at rest in the chosen position; (b) defense against the spread of infection by keeping the cellular infiltration undisturbed in the tissues and lymph channels round the wound. (5) This is favored by a particular technic of enclosure of the wound in that part of the plaster which covers the exposed tissues. It should apply an even gentle pressure similar to that normally exercised by the fascia and the skin. (6) The closed plaster treatment eliminates frequent dressings, which mean either pain or repeated anesthesia for the patient and are both time consuming and expensive.

According to some surgeons, it is believed that after 2 or 3 days the closed plaster method is not applicable to a dirty wound because excision is no longer practicable. According to Girdlestone, this is a great mistake, for in his opinion no method of treating can compare with closed plaster after saucerization, which may include laying open all heavily infected areas. He believes that a wound that will benefit from saucerization and enclosure does not always need excision; indeed, excision is generally contraindicated in the presence of *established sepsis*. The method

has been decried because a number of wounded men have reached the hospital with wounds doing badly from extensive pressure sores. According to Girdlestone, the surgeons probably were imperfectly familiar with the method. He believes that properly used, the plaster treatment of wounds has its advantages and place in the treatment of war wounds.

**"Soil Bacteria Extract Solution"—  
A New Germicide for War Wounds**

—McDonald<sup>19, 20</sup> reports from the Biochemical Research Foundation of the Franklin Institute of Philadelphia, that a new germicide has been discovered which is not only very specific for *gram-positive microorganisms* such as streptococci and staphylococci, but also for *Cl. sporogenes*, *Cl. histolyticum* and *Cl. welchii*. These latter organisms are the chief ones found in *gas gangrene* infections.

Strangely enough, the new germicide is the product of *soil* which is so often infected with the organisms of *gas gangrene*. The active substance, incompletely identified as yet, is made from the dried extract of cultures of soil bacteria and is simply termed "*soil bacteria extract*."

Hoogerheide,<sup>21, 22</sup> after working for several years with different species of soil bacilli, found several species which were *antagonistic to gram-positive organisms*, including spore-bearing and tuberculosis bacilli as well as lepra bacilli.

By growing certain soil bacilli in a liquid medium he was able to obtain from the liquid culture, by filtration and alcoholic extraction, a *fine crystalline powder* which was highly lethal to gram-positive germs. The intraperitoneal injection of as little as 0.02 mg. afforded protection to mice which had been injected with 1,000,000 lethal doses

of virulent pneumococci or with 1000 lethal doses of anthrax organisms. *In vivo*, he found that only 0.00001 mg. (0.01 gamma) per cubic centimeter of liquid medium was required to inhibit the growth of *Gaffkya tetragena* and 0.0005 mg. to inhibit *Staphylococcus aureus*.

Tested clinically in human infections, it was found to heal extensive infections caused by gram-positive organisms in a remarkably short time and, in addition, to possess some unknown substance which *stimulated wound healing* in burns and skin grafts.

Murray Wright<sup>19, 21</sup> has reported the use of this new agent in numerous cases, including *gas gangrene of the thigh* (*Cl. welchii*), *carbuncles* and *breast abscesses* (staphylococci and streptococci), *suppurative arthritis* (pneumococci) infected *carcinomas of the foot, thigh and lung* (staphylococci and streptococci), *osteomyelitis* (staphylococci), *infected burns, skin grafts*, etc.

In each case to be treated, a culture is made of the infected lesion to determine the causative organism or organisms. For quick and approximate determination, a swab from pus can be smeared on a microscopic slide and the same be stained by the Gram method in a few minutes.

Superficial lesions are treated by daily dressings of sterile gauze dipped into an aqueous solution of the crystalline extract which has previously been dissolved in a few cubic centimeters of alcohol. Deep lesions are treated with weaker dilutions instilled into the depths of the wound by the drip method of Carrel-Dakin.

Intravenous injections of a solution of the extract have been made into animals previously infected with various organisms but experiments thus far have shown that the crude extract, which con-

tains several fractions, is at present too toxic for parenteral use.

*In vitro* and *in vivo* (laboratory mice) Hoogerheide found that "soil bacteria extract solution" killed *B. anthracis* and protected mice which had been infected with the same. As yet, it has not been used clinically in cases of human anthrax.

Several of the promising factors of this new germicide are: (1) Its lack of any coagulating effect upon protein tissues which renders many ordinary chemical antiseptics partially inactive. (2) The presence of an unknown substance which stimulates wound healing. (3) The minuteness of the amount of the product required for germicidal purposes ( $\frac{1}{100,000}$  aqueous solution) which facilitates military or naval transport of material as was evidenced recently when a small package, of the dried powder, was sent by plane to England. This package which could be carried in one's pocket, when dissolved in distilled water was sufficient to make several barrels of solution for treating British wounded soldiers and civilians.

**Sulfonamides**—Military and naval officers will be interested to learn that the British War Office has issued a memorandum on the use of the sulfonamide derivatives for the guidance of army medical officers which is of wide interest, for it has been compiled by leading experts and is the last word on the subject.<sup>23</sup> It is recommended that *sulfapyridine* should be given in *gonorrhea*, *cerebrospinal fever*, *pneumococcic infections*, *staphylococcic septicemia* and *gas gangrene*. *Sulfanilamide* is recommended as the drug of choice in the prophylaxis of *wound infection* and the treatment of *erysipelas*, *cellulitis*, *meningococcus carriers*, the *acute phase of wounds* known to be *infected with hemolytic*

*streptococci*, *follicular tonsillitis*, *otitis media* and *Bacillus coli urinary infections*.

The principle of effective treatment is to obtain a high blood concentration as rapidly as possible and to maintain this for a time. As the drugs are rapidly excreted, administration should be 4-hourly, day and night. For maintaining a steady blood concentration the oral route is the best and ordinarily should be followed. A soluble preparation for injection is used in cases where oral administration is impossible or inadvisable. For established or developing infections, courses of treatment should seldom exceed 10 days. As a rule, when infection is amenable to these drugs the result is rapid.

*Infections Due to Streptococci and Gas Gangrene Bacilli*—A prophylactic course of *sulfanilamide* should be given to all wounded persons where there is reason to fear septic infection or gas gangrene. This should be started as soon as possible and continued for at least 4 days to protect the patient against the risk of later infection by streptococci in the hospital. Prophylactic treatment may be administered orally or by local application to the wound. For *prophylaxis* the first dose should be 23 grains (1.5 Gm.) of sulfanilamide. Two hours later 4-hourly administrations of  $7\frac{1}{2}$  grains (0.5 Gm.) should begin and they should be continued for 4 days. If it is feared that *gas gangrene* is beginning, the first 2 doses should be *doubled*.

When gas gangrene or severe streptococcic infection is definitely established, the first dose of sulfanilamide or sulfapyridine should be 30 grains (2 Gm.). Subsequent doses, starting 2 hours later and continuing at 4-hourly intervals, should be 15 grains (1 Gm.). After 2 days, as the condition improves, the

interval may be prolonged, but not to more than 6 hours, for several days. After the temperature becomes normal, small doses (45 grains—3 Gm—daily) should be continued for 3 or 4 days.

**X-ray Treatment**—According to Keating and Davis,<sup>24</sup> the primary requisite of military surgery is to send the wounded back to duty as quickly as possible and with the least possible mutilation. They believe that such treatment differs from its civilian prototype mostly in that it usually cannot be instituted quickly because of evacuating difficulties. Experience during the past 2 years has shown that prophylactic Roentgen treatment in industrial cases of penetrating, perforating and crushing wounds, given a *few hours after their reception*, perceptibly decreases the percentage of infections by gas-forming organisms, as well as by streptococci and staphylococci. Keating and Davis believe that this prophylactic treatment of dirty wounds, in addition to the accepted cleansing and débridement, makes primary closure a frequent success and is frequently successful even if fractures are plated immediately. Naturally, to make this type of treatment available to soldiers in the field, it will be necessary to install adequate x-ray apparatus at the first well-equipped surgical establishment through which the wounded are passed and operated on during their evacuation to the rear. It is suggested that these prophylactic x-ray units be placed in the mobile surgical hospitals. Though the writers advocate early x-ray therapy in the treatment of potentially infected wounds,

general surgeons at large have not, as yet, been favorably impressed by the results of irradiation. If adequate drainage, immobilization, etc., have been previously carried out, however, prophylactic x-ray treatment may well be indicated for its supposed effect on spore-bearing organisms.

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# THERAPEUTICS

By HENRY K. MOHLER, M.D.

## ALUMINUM HYDROXIDE

In the treatment of *peptic ulcer* it is desirable to achieve 3 purposes, *i. e.*, (1) relieve pain, (2) relieve pylorospasm, (3) reduce acidity, thereby avoiding digestion and corrosion and presumably facilitating healing. This is the underlying rationale of the Sippy regimen and its many modifications. The introduction of colloidal aluminum hydroxide represents an important addition to alkali therapy. It is slightly astringent, has a definite adsorptive power, has high buffering capacity. It is not absorbed, does not affect acid-base metabolism and is nontoxic. It does not alter mineral metabolism.

When treatment is begun, the patient is put at bed-rest with bathroom privileges, and a continuous intragastric drip set up, using 1 part of colloidal aluminum hydroxide gel to 3 parts of water. The rate of flow is established at 15 to 25 drops per minute, and this is continued from 7 to 14 days, depending on the size of the ulcer, severity of symptoms, and the presence of bleeding. All patients except those with active bleeding are permitted 3 to 5 daily small feedings of milk, soft cooked eggs, cooked cereals, creamed soups, etc. Sedatives are employed in the usual manner. A few drops of a nasal oil is instilled into each nostril 3 or 4 times daily to prevent local irritation. After the patient becomes ambulatory, the usual ulcer regimen is followed, and instead of the customary alkaline powders, 1 to 2 drams (4 to 8 Gm.) of the colloidal aluminum hydroxide gel is given in  $\frac{1}{3}$  glassful of water, an hour after each meal and at bedtime. After a month, the dietary restrictions may be gradually reduced, al-

though alcohol, highly seasoned foods and tobacco are always interdicted.

At the Jefferson Hospital, Eads<sup>1</sup> studied 40 patients treated by this method. Thirty-one had not been relieved by the usual medical treatment, and 6 were actively bleeding at the time therapy was begun. All but 2 secured prompt symptomatic relief, and there was clinical and roentgenological evidence of rapid healing.

A note of warning must be sounded. This drug has a marked tendency to produce *constipation*, and in a few cases, especially where it has been necessary to use morphine repeatedly, fecal impactions have been reported. To obviate this danger, *mineral oil* should be prescribed in sufficient quantity, or a preparation used which already contains it.

This method of therapy by no means replaces the hitherto accepted modes of treatment, but does constitute a valuable addition.

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## AMPHETAMINE SULFATE

### (Benzedrine Sulfate)

It has been a well-known effect of amphetamine sulfate that it reduces the appetite for food. Beyer has shown that when  $\frac{1}{2}$  grain (30 mg.) is given orally there is an average metabolic increase (under basal conditions) of 15.4 per cent within  $2\frac{1}{2}$  hours; the metabolic rate does not return to normal after 9 hours, but does within 24 hours. These 2 factors would point to the application of this drug in the treatment of *exogenous obesity*. Ersner<sup>2</sup> has used amphetamine with success in the treatment of over 500 cases and has noted no seriously harmful effects therefrom. A rational proce-



dures which might be followed would entail, of course, a complete and thorough physical examination, care being exercised to search for evidence of endocrine imbalance. A diet of 1200 to 1500 calories per day (depending on age, height, and pursuits of patient) is provided. Fluid intake should be adequate but limited. Daily evacuation of the bowels should be provided for, it being remembered that amphetamine tends to produce intestinal stasis.

The dosage of amphetamine sulfate should be outlined for weekly periods only, and thus insure regular check-ups. Ernster's<sup>2</sup> practice is to use initially the smallest possible dose 3 times daily after meals. At the end of 1 month, or if 20 pounds (9 kg.) have been lost prior to that time, the drug is stopped for 1 week and vitamins prescribed (B, C, and G) to supplement the diet which often is deficient. Thereafter, this routine is repeated every month, or whenever 15 additional pounds (7 kg.) have been lost. During the course of treatment, the dosage of amphetamine is gradually increased, after every week's rest period the last prescribed dosage being resumed, so that within 3 months the patient is taking  $\frac{1}{8}$  grain (10 mg.) of amphetamine sulfate 3 times daily. The average weight loss for his series was  $3\frac{1}{2}$  pounds (1.4 kg.) per week, and the total weight loss limited to one-fifth or one-sixth of the body weight during a course of treatment.

It has been noted that, despite the pressor effect of the drug, some patients with mild or moderate hypertension enjoy a return to normal blood-pressure ranges. This is in accord with a frequently made observation that reduction of obesity is often of value in the treatment of hypertension.

The use of this drug entails caution, especially in those who already suffer

cardiovascular damage; under careful scrutiny, it should prove a valuable adjunct in the treatment of exogenous obesity.

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## ARSENIC

### Neoarsphenamine and Mapharsen

The accepted present method of *antiluetic therapy* comprising the alternate use of an arsenical and a heavy metal in continuous courses over a 2-year period is expensive, time-consuming, and awkward in its application. It requires the co-operation of the patient over a long period. The human vessel is noted for its frailty, and too often the treatment is inadequate because it ceases when the pressing symptoms or external stigmas disappear. Because of the promise of quick cure, and the guarantee of rapid sterilization of contagious lues, there is great interest in the use of neoarsphenamine and mapharsen in massive dose by the intravenous drip method. Recently, Hyman, Chargin and Leifer<sup>3</sup> (the progenitors of the method) published the results of their 5 years' observation. Of the group treated with neoarsphenamine, 67 were adequately followed for a 5-year period. Of this number 86 per cent were clinically cured and had complete, persistent seroreversal.

The Council on Pharmacy and Chemistry<sup>4</sup> of the American Medical Association reviewed the present status of this method of arsenotherapy. Neoarsphenamine has given way to mapharsen because of its greater safety. In the series of 111 treated with neoarsphenamine, there was 1 death; while none occurred in 283 cases given mapharsen. The relative appearance of toxic effects in the 2 groups are conveniently tabulated on the following page.

**Technic**—A total of 18 grains (1.2 Gm.) of mapharsen is given in 5 days. There are

	<i>Neocarsphenamine</i>	<i>Mapharsen</i>
Total treatment courses.	.... 111	283
1. Primary fevers .. .	69 (62%)	115 (41%)
2. Secondary fevers . . .	71 (64%)	35 (12%)
3. Toxicodermas . . . . .	50 (45%)	32 (11%)
4. Dermatitis exfoliativa . . . . .	1* (0.9%)	0
5. Blood dyscrasias . . . . .	0	0
6. Renal damage . . . . .	0	0
7. Jaundice . . . . .	4 (3.6%)	2 (0.7%)
8. Peripheral neuritis . . . . .	39 (35%)	5 (mild) (1.7%)
9. Cerebral symptoms (total)...	2 (1.8%)	3 (1.06%)
(a) Hemorrhagic encephalitis . . . . .	1 (0.9%)	1 (0.35%)
(b) Single convulsion . . . . .	1 (0.9%)	1 (0.35%)
(c) Disorientation . . . . .	0	1 (0.35%)
10. Fatality . . . . .	1 (0.9%)	0

\* Received sulfanilamide for complicating gonorrhea.

several methods of administration, the most practicable being as follows: The solution should be prepared in the morning immediately prior to its use, dissolving  $3\frac{3}{4}$  grains (0.24 Gm.) of *mapharsen* in 2 quarts (2000 cc.) of 5 per cent *glucose* (dextrose); a standard intravenous drip is set up, and the rate of flow so regulated as to require 10 to 12 hours for the total volume (*i. e.*, no faster than 200 cc. per hour) to flow. If there is a rise in temperature to 101.4° F. (38.5° C.) or more (which usually occurs within 6 to 8 hours), therapy is immediately stopped, and the insufficient dosage compensated for by distributing the equivalent lacking to complete the first day's treatment over the remaining 3 or 4 days in equally divided quantity. Thus, if there was a lack of  $1\frac{1}{2}$  grains (0.09 Gm.) on the first day, then  $\frac{1}{2}$  grain (0.03 Gm.) should be added to the  $3\frac{3}{4}$  or 4 grains (0.24 or 0.26 Gm.) in all given daily on the second, third, and fourth days, and  $3\frac{3}{4}$  grains (0.24 Gm.) on the fifth. If jaundice appears, treatment should be discontinued.

This manner of treatment is not recommended to be substituted for the present well-established one. The appearance of cerebral symptoms in 3 cases of 283 treated, at least 1 of which was hemorrhagic encephalitis, is a reminder of the attendant danger, and the experimental status of this procedure dictates that it be undertaken only in suitable

institutions. That it may mark a forward stride in syphilis therapy compels the Reviewer's interest.

The toxic manifestations parallel those already well-recognized in arsenotherapy. Their relative incidence naturally varies because of the massive dosage. Whether Ehrlich's hope for "*therapia magna sterilans*" has been or can be achieved, time will tell. The final report of the COMMITTEE ON MASSIVE DRIP INTRAVENOUS THERAPY of the Council on Pharmacy and Chemistry is to be eagerly awaited.

## BISMUTH

### Sobisminol

**Description**—Sobisminol mass, the reaction product of sodium bismuthate 0.2 Gm., tri-isopropanolamine 0.4 Gm., propylene glycol 0.1 Gm., and ethyl alcohol 0.1 Gm., represents about 150 mg. of elementary bismuth.

It occurs as a red-brown or chocolate-brown, paste-like mass, with an odor resembling that of tri-isopropanolamine alone, and a bitter taste with a sweetish, metallic after-taste. It is soluble in water and alcohol; partially soluble in ether

and acetone. One gram of sobisminol mass dissolved in distilled water to 10 cc. should produce a pH not above 11.9.

**Physiological Action**—It has been shown that when given orally in daily doses representing 13 grains (0.84 Gm.) of bismuth, a sufficient amount of therapeutically active bismuth is absorbed from the gastrointestinal tract to produce the regression of active luetic skin lesions. It will produce involution in primary and secondary *lues* almost as rapidly as neoarsphenamine. The evidence at present indicates that it produces satisfactory bismuth levels in the blood stream and is as useful as any other bismuth preparation. The only *untoward reactions* noted thus far are mild gastrointestinal disturbances which only occasionally become so severe as to necessitate the discontinuance of its use. This does not represent any drastic departure in the antiluetic regimen, since courses of bismuth and an arsenical should be alternated. From a public health standpoint, it may be thought an undesirable preparation, since it may encourage self-medication and lends itself to easy exploitation. It possesses advantages in that it obviates the need for intramuscular injections of bismuth with its attendant small, though ever present dangers. The final estimation of the therapeutic status of sobisminol must await the passage of time which will permit the collection of sufficiently extensive and accurate statistics, but it is clearly evident that it is a potent and antiluetic drug.

**Dosage**—Each capsule of 12 grains (0.75 Gm.) sobisminol mass represents about  $2\frac{1}{3}$  grains (150 mg.) of metallic bismuth. The usual dosage employed is 2 or 3 capsules, 3 times daily, with water, after meals.

**Untoward Effects**—Toxic manifestations are those of other bismuth preparations, *i. e.*, skin eruptions (pruritus, erythema, dermatitis, purpuric rash) blue gum line, gastric disturbances, stomatitis, headache, nausea, etc.

### Sobisminol Solution

Sobisminol solution represents the reaction product of sodium bismuthate, tri-isopropanolamine and propylene glycol and water. Each cubic centimeter represents about 20 mg. of metallic bismuth and 0.5 cc. of propylene glycol. It is a clear, dark, brownish-red liquid with an odor resembling that of tri-isopropanolamine and a sweet metallic taste. It readily mixes with equal parts of water or alcohol.

**Dosage**—This consists of 16 to 32 minims (1 to 2 cc.) given intramuscularly into the buttocks twice weekly. It has been proposed in the treatment of all types of syphilis as one of the several preparations of injectable bismuth available. Whether or not it possesses advantages over the hitherto more commonly used compounds cannot be stated.

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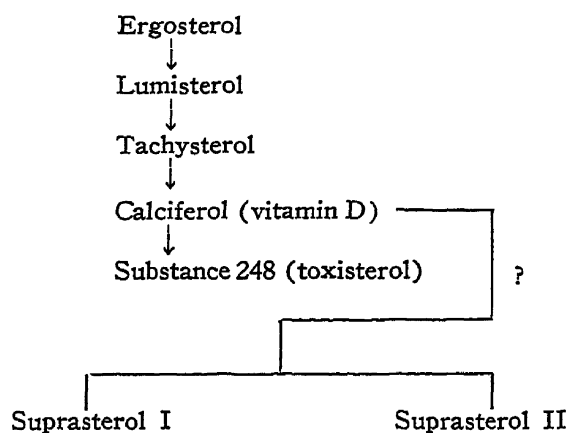
### CYCLOPROPANE

Meyer and Schotz<sup>5</sup> suggested that in cases of **intractable bronchial asthma** where other measures have failed and general anesthesia is deemed necessary, cyclopropane may be the agent of choice because of its high oxygen content which will tend to relieve anoxia. It is not as irritating to the bronchial mucosa as ether, and because of the rapidity of inducing anesthesia, it tends to minimize struggling. It would be well to bear this suggestion in mind, but it is only infrequently necessary to seek recourse to a general anesthetic in the treatment of bronchial asthma.

## DIHYDROTACHYSTEROL (A.T. 10)

Holtz in 1933 first used dihydrotachysterol (*"antitetanisches Präparat Nr. 10"*) in the treatment of **parathyroid tetany** in Germany. As its efficacy in this disease has been repeatedly substantiated, interest has grown because it is active perorally.

**Description**—Dihydrotachysterol is a photochemical derivative of ergosterol. Its relation to similar sterols produced by ultraviolet irradiation of ergosterol can be seen in the schema of Setz which has been modified by Bills <sup>6</sup>



A.T. 10 is chemically converted tachysterol, to the end that it may be suitable for oral use.

**Physiological Action**—The consensus of opinion is that dihydrotachysterol has no antirachitic effect. Its fundamental action is to increase the absorption of calcium from the intestinal tract, and increase the urinary phosphorus excretion—with consequent rise in serum calcium levels and fall in inorganic serum phosphorus. The action of dihydrotachysterol resembles that of vitamin D, but acts much more rapidly, and is much less sustained; it differs from parathyroid hormone, which evidently does not primarily affect intestinal calcium absorption.

The clinically used preparation is a 0.5 per cent solution in sesame oil. The effect of the preparation is cumulative, and continued excessive dosage produces hypercalcemia, hypophosphatemia, extensive calcification, renal calculi, anorexia, loss of weight, hypotonia, and lassitude. In proper dosage, there is no observable detriment in its continued use. The requirement of dihydrotachysterol in those suffering from hypoparathyroidism seems to be increased by menstruation, physical exertion, pregnancy, and other causes of increased metabolism. Its use prevents the formation of lenticular cataracts which result from continued hypocalcemia, but will not cause the cataracts, once formed, to regress. Its effects are said to be counteracted by estrogen and androgen.

**Indications**—Its only acceptable indication at present is in the treatment of **parathyroid deficiency**. Its advantages are that it exercises no selective effect on diffusible or nondiffusible calcium, provides rapid action, is given orally, requires no dietary restriction (low phosphorus diets are usually not necessary) and usually requires only small dosage for maintenance. Unfortunately, it is quite expensive at present.

**Dosage and Manner of Administration**—The dosage required varies with each individual case. Usually 6 to 10 cc. are given the first day, 4 to 8 cc. the second, and 2 to 4 cc. the third. Maintenance is usually satisfactory with 0.5 to 2 cc. daily. When the patient first undergoes treatment and standardization is required, the daily total is divided into 3 or 4 equal doses, given  $\frac{1}{2}$  hour before meals, and the calcium serum levels are determined daily, dosage being regulated accordingly. Since the chief action is increased calcium absorption, *calcium gluconate* or *calcium lactate* 30 grains (2 Gm.) is given an hour before meals.

When a satisfactory serum calcium (9 to 11 mg. per 100 cc.) is achieved, the dose is decreased to a maintenance level, which may range from 2 cc. daily to 0.5 cc. every second or third day, calcium administration being continued. The patient should remain under continued observation, since altered metabolism may require increased doses or the cumulative action of the drug may produce a hypocalcemia.

### DILANTIN SODIUM

**Description**—Dilantin sodium (sodium 5.5-diphenyl hydantoinate) is described (NNR, 1940) as an odorless, white, microcrystalline powder with a slightly bitter taste. It is soluble in alcohol and glacial acetic acid, and insoluble in ether, petroleum ether, benzene. Aqueous solutions of dilantin sodium yield an opalescent, crystalline precipitate of di-phenylhydantoin which dissolves when the pH of the mixture is adjusted to 11.7.

**Physiological Action**—Dilantin sodium is a derivative of glyceryl urea whose mode of action, intermediate metabolism and excretion are not known. Its principal effect is exhibited as a relatively strong anticonvulsant with mild hypnotic and depressant powers.

Yaskin and Drake,<sup>7</sup> of the Jefferson Hospital, studied the effect of dilantin sodium on the ascorbic acid blood serum level of 20 patients. They were all under a controlled diet containing  $1\frac{1}{6}$  grains (75 mg.) of vitamin C for the entire duration of the study, including a control period. These patients were divided into 3 groups: The first (5 patients) received 15 grains (0.9 Gm.) dilantin daily; the second group of 5 patients received 10 grains (0.6 Gm.) dilantin daily; and the third group of 10 patients

received 5 grains (0.3 Gm.) dilantin daily.

The conclusions from these studies were as follows:

- 1 Dilantin sodium definitely depresses the ascorbic acid serum level in humans, and the greater the dose the quicker did this depletion occur.

2. The first 2 groups of patients (0.9 and 0.6) all developed severe symptoms referable to the central nervous system within 2 weeks after the onset of the drug. The depression of the vitamin C in the serum had no relationship to the onset of toxic symptoms; therefore, in large doses the drug is intrinsically toxic.

3. Three weeks after onset of administration, 65 per cent of the patients developed hyperplasia of the gums in varying degrees of severity. No relationship could be established between the degree of deficiency of vitamin C in the plasma and the occurrence or degree of the developing hypertrophic gingivitis.

4. In increased doses dilantin sodium is a toxic drug.

Whether the effects noted are due to impaired absorption of vitamin C, or to increased metabolism, has not been demonstrated as yet.

**Untoward Effects**—Its toxic manifestations, in common with phenobarbital, are lethargy, ataxia, anorexia, nystagmus, and fine tremors of the hands. Unlike phenobarbital, it also produces epigastric distress, ocular pain, diplopia, blurred vision, vertigo, and gingival hyperplasia. In common with many drugs, it can produce a dermatitis of varying severity, and much less often a pronounced purpuric reaction. The toxic nervous symptoms are so numerous and variegated as to defy classification. The therapeutic and toxic doses are close and this leaves but a small margin of safety. With continued use, there is apt to be decreased tolerance or late toxic effects.

**Indications**—At the present, its use should be restricted to the treatment of *epileptic patients* who are not benefited by the commonly used barbiturates or

bromides, or in whom these drugs induce undesirable side-effects. The reaction of dilantin sodium on any given patient is not predictable. In a series of patients who were adequately studied, 30 per cent were markedly improved, 30 per cent were slightly improved, 25 per cent were unchanged, and 15 per cent were definitely worse. Williams<sup>8</sup> reports that 36 per cent of his patients manifested some toxic symptoms. It appears that its greatest usefulness lies in the treatment of *grand mal*, and that it does not influence the mental deterioration often observed in epileptics.

**Dosage**—In adults, the 1½-grain (0.1 Gm.) capsule should be given 1 to 3 times daily, preferably after meals, with at least ½ glassful of water to minimize gastric irritation (dilantin sodium being strongly alkaline). If necessary, the dose may be raised gradually under careful supervision to 3 grains (0.2 Gm.) 3 times daily, but this increase should be made only when absolutely necessary. Where the patient has already been undergoing previous therapy, the transition should be made gradually, replacing 1 dose of the drug previously employed with 1 capsule of dilantin sodium (1½ grain—0.1 Gm.) every other day so that in 6 days there has been total substitution. It may be deemed wise to supplement dilantin with bromides or small doses of phenobarbital. Children under 6 years of age should be started out with ½ grain (0.03 Gm.), twice daily, mixed with fruit juice, milk or cream, and the dose increased as needed with the most scrupulous care. If mild toxic manifestations appear, there should be a 2 or 3 days' rest period, after which dilantin sodium may again be started.

The evaluation of dilantin sodium in the treatment of epilepsy must await the verdict of time.

## HEPARIN

**History**—Heparin, the physiologic anticoagulant, demonstrates the processes of modern research. First noted in 1916 by McLean, who was working in Howell's laboratory on the problem of thromboplastic action of cephalin, it has come a long way to fall within the eager reach of applied medicine. Howell and Holt coined its name in a paper on heparin and proantithrombin in 1918, the term being chosen to indicate its genesis in the liver. The material prepared at that time from the ether-soluble fraction of dried dog liver was crude, but it prevented clotting. In 1923, 1925, and again in 1928, Howell demonstrated improvements of technic to produce a purer, more potent material, and showed that the former conception of a heparphosphatid was in error, since there was no phosphorus in the refined material.

**Description**—It seems evident, at present, that heparin occurs in minute quantity in the flowing blood and maintains it in its liquid state. According to the well-known Howell theory of coagulation, cephalin (liberated from the blood-platelets or injured tissue) combines with heparin, releasing labile prothrombin, which in the presence of calcium ions forms thrombin, which in turn converts fibrinogen to fibrin. *Diagrammatically,*

Prothrombin — antiprothrombin (heparin) + cephalin → prothrombin + Ca<sup>++</sup> → thrombin + fibrinogen → fibrin.

While this formula does not provide a full exposition of Howell's theory nor explain all the observed phenomena, it provides a rough scaffold to support understanding. Contrariwise, there is evidence that heparin (Mellanby, and Quick<sup>9</sup>) may act as an antithrombin. There is still another view that heparin acts as an anticoagulant by its ability to

activate an antithrombin precursor. None of these conceptions suffice to explain all the known facts, nor are they mutually compatible, hence the existent state of confusion.

There has been a large amount of work reported covering the isolation of heparin from liver, lung and other tissues, and considerable differences of opinion regarding its chemical composition, which include variables due to the manner of preparation. The evidence of the occurrence of heparin in the mast-cells of Ehrlich has received considerable attention and would explain differences in clotting of blood at various sites in the body (*i. e.*, the cornea). Suffice it for present purposes to consider heparin as a mixture of natural *mucoimpolysulfuric esters*. It has been found that heparin possesses a strong negative electric charge and therefore is able to markedly influence a colloidal system. Heavy metals, especially the silver ion, will accelerate clot formation in heparinized plasma. Protamine combines with heparin stoichiometrically (1 mg protamine · 0.3 mg. heparin) and neutralizes its anticoagulant power. The reaction of toluidine blue with heparin seems to be that of the granules in the Ehrlich mast-cell.

Physiologically, heparin may, at least at this time, be considered the product of certain specialized cells which enters the blood stream and prevents clotting. Further, heparin inhibits complement, but the mechanism involved and the factors concerned are obscure. There is no "negative phase" after the administration of heparin, coagulation time returning to the normal limits of the animal. Heparin, given in single doses, will temporarily delay the formation of thrombi after experimental vascular injury; in repeated doses or when given by continuous intravenous drip, in many cases it will permit repair without thrombus formation.

A most interesting communication by Thalhimer, Solandt, and Best<sup>10</sup> reports the continuous exchange of blood between 2 dogs, one of which had undergone bilateral nephrectomy, the procedure being rendered possible by the use of a special pump and pure heparin. There is evidence to indicate that heparin plays a rôle in anaphylactic shock, but whether it tends to promote or prevent it cannot be said. In tissue cultures, heparin appears to inhibit growth and promote differentiation. Heparin halts adsorption of colloid metals by the reticulo-endothelial cells without apparent cell damage. Heparin does not produce the increased clotting time in certain types of jaundice, this effect being due to the lack of vitamin K. It is known that heparin is inactivated by serum *in vitro*, but its catabolism in the body is unknown.

**Standardization and Dosage**—The standardization of heparin was originally a pragmatic one, because of the discrepancies in potency. The original Howell unit was that amount which prevented 1 cc. of cat's blood from coagulating for 24 hours. Best and his co-workers consider a unit 1/100 mg. of the crystalline barium salt of purified heparin as prepared by Charles and Scott; this is roughly 5 times the cat unit of Howell. If and when a standard preparation of heparin becomes available, it would be well to designate merely the weight of the product employed.

The partially purified heparin often displayed untoward reactions—such as chills and fever, precipitate fall in blood-pressure, headache. The use of purified heparin is quite safe, even in large doses. Heparin itself is apparently nontoxic.

The effect upon the coagulation time varies with the size of the dose, the frequency with which it is given, and with different individuals. When used clin-

ically to prevent coagulation, it is best administered by means of the intravenous drip, a definite quantity (*i. e.*,  $1\frac{1}{2}$  grains—100 mg.—dissolved in 500 or 1000 cc. of sterile physiological salt solution, being 10,000 units of the Toronto material) and dosage controlled by regulating the rate of flow of the solution. This is done by frequent measurements of venous clotting time. Thus, to maintain the venous clotting time at about 3 times normal, Kelson and White<sup>11</sup> used a solution of 2000 units per 100 cc. at a flow rate of 15 to 25 drops per minute, the rate being adjusted in accordance with the clotting values.

Heparin may be sterilized by autoclaving at 110° C. for 30 minutes, or by boiling. Solutions may be stored in sealed ampoules indefinitely.

**Uses**—Since purified heparin has no demonstrable effect on man other than on coagulation and bleeding time, sedimentation rate, and an obscurely defined effect on complement, its clinical uses may proceed apace.

#### **Transfusion:**

1. Direct—Moistening implements and conducting tubing with heparin solution.

2. Indirect—As a substitute for sodium citrate, 3 to 4 mg. of purified heparin per 100 cc. of blood.

3. Heparinization of the donor—1 mg. per kilogram body weight administered 10 minutes before transfusion is started. This will raise the clotting time to 15 to 30 minutes, and the effect persists for several hours, gradually diminishing.

**Surgery**—It is to be remembered that heparin *will not* dissolve a blood clot either *in vitro* or *in vivo*. Some hours after operation (generally from 4 to 24), when all hemorrhage and ooze has stopped, it is perfectly safe to administer heparin to the patient to avoid thrombus formation. This, in the experience

of Murray and Best<sup>12</sup> with 355 cases, is particularly indicated as follows:

1 After splenectomy, where the postoperative platelet rise tends to promote thrombus formation.

2 After a diagnosis of pulmonary embolism has been made, to prevent the formation of further thrombi, and to prevent the further extension of the thrombus which has lodged in the lung.

3 In the treatment of spontaneous thrombophlebitis. Murray and Best believe treatment should be continued until the patient has returned to normal activity.

4 After vascular surgery, such as embolectomy, arteriorrhaphy, etc.

It is thought that heparin will be a stimulus to further the development of cardiac surgery, since it would be possible to prevent the formation of mural thrombi.

**Internal Medicine**—The development of effective chemotherapeutic agents occurring at about the same time that purified heparin and its effects were receiving wide attention, suggested that a weapon might be at hand to attack **subacute bacterial endocarditis**. Kelson and White<sup>11</sup> published a preliminary report in 1939 in which they reported the use of sulfapyridine and heparin on 6 cases of **subacute** and 1 case of **acute endocarditis**. Since then there have been several scattered reports. There is the danger of hemorrhage following the impaction of small emboli in the brain because of impaired coagulation, but the prognosis in subacute bacterial endocarditis justifies any rational measures. The rationale of this therapy in all probability is that chemical attack aiding natural immune responses will sterilize the blood stream, while the heparin will prevent further thrombotic deposit in the vegetation, tend to prevent embolism (from fresh thrombi), prevent the growth of vegetations, and thereby permit healing and fibrosis. Before heparin



therapy is instituted in any case, the diagnosis should be made unequivocally, the organism identified in culture, and the appropriate sulfonamide chosen and administered in the usual therapeutic dosage. The method pursued by Kelson and White may be outlined as follows:

1. Heparinization is begun 4 to 7 days after the institution of sulfonamide therapy.

2. Ten cubic centimeters of heparin are added to 500 cc of physiologic sodium chloride solution and the solution given intravenously by continuous drip for 14 days and nights. The rate of flow (usually 15 to 25 drops per minute) is so regulated as to maintain venous clotting time at about 1 hour (3 times normal limit).

3. Clotting time is measured at regular intervals to guide heparin administration (twice daily, or more often as indicated).

4. Three grains (200 mg) of ascorbic acid is given 4 times daily for 3 days and then continued at the rate of 1½ grains (100 mg.) per day.

5. Blood transfusions are given as and when indicated.

6. Sulfonamide therapy is continued for 1 week after the cessation of heparinization

The number of cases so treated and reported are few. Mishaps have occurred. Untoward reactions have been noted from the use of an impure lot of heparin. Autopsy studies have, however, in several instances given clear-cut evidence of healing.

Much more work will have to be done, and observations continued over a sufficient period to establish the validity of "cures." Few men have hitherto been fortunate enough to ever see a "cured" case of subacute bacterial endocarditis, and this procedure theoretically promises more than any other. In competent hands, it is worthy of trial.

There remain 2 more conditions in which the early use of heparin is theoretically advantageous, these being early *cerebral thrombosis* or *embolus*, and early *coronary occlusion*.

The reasoning behind the employment of heparin in these cases is the prevention of extension of the thrombus, thus limiting the area of infarction. No clinical reports concerning this application of heparin are available.

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## HISTAMINE

The rôle of histamine in various allergic manifestations is well-established though ill-defined. It has been noted, particularly in urticaria and in cold sensitivity, that desensitization with histamine is possible, and that the use of a specific enzyme, histaminase, will vitiate histamine action. Horton and his colleagues<sup>13</sup> recently have described a syndrome of vascular headache which has been termed "*histaminic cephalalgia*" and which may be successfully treated by histamine desensitization.

The type of cephalalgia amenable to this mode of therapy is evidently a distinct clinical entity. There is unilateral headache, usually having its onset in the second half of life. It has a sudden onset and offset, coming on often at night and awakening the sufferer. It is accompanied by lacrimation and turgescence of the eye, rhinorrhea or congestion of the nostril, and quite often swelling of the temporal vessels. All these associative phenomena occur on the involved side of the head. There is usually increased skin temperature as well on the same side of the head, face, and possibly neck.

The headache itself is severe, is prone to frequent recurrence, and in its distribution parallels no particular nerve paths. Tenderness on pressure over the external and common carotid arteries has been noted, and this pressure may thereafter be followed by cessation of pain.

Horton<sup>14</sup> reported the use of histamine in 112 cases of headache, 72 of which were categorized as histamine cephalalgia. It was noted that this type of headache could often be prevented by refraining from lying down. The headache could be exactly reproduced by the injection of histamine subcutaneously in doses of 0.1 to 0.2 mg., and it was observed that epinephrine gave prompt relief.

The mode of treatment followed by Horton entails the use of histamine diphosphate (0.275 mg. per cubic centimeter being equivalent to 0.1 mg. of histamine base). Injections are given subcutaneously twice daily from 10 to 21 days, starting with 0.25 cc. and increasing each successive dose by 0.05 cc. until at the sixteenth injection the patient is receiving 1 cc. Thereafter the dose is maintained at 1 cc. If there is slight flushing or other indications of drug response, the dose should be halved and thereafter slowly increased. When all attacks have ceased, maintenance is provided by injections of 1 cc. each, given subcutaneously from 1 to 3 times weekly.

Horton<sup>14</sup> also reports favorably on the use of *histaminase* in treating this syndrome, obtaining satisfactory results in 8 of 9 patients so treated. The question of the therapeutic efficiency of histaminase in this, as in other allergic states, is a much mooted one, and it is the part of wisdom to hold judgment in abeyance.

### LIVER EXTRACT

Cheney<sup>15</sup> has reported the use of liver extract (*reticulogen*) as being effective in securing a remission in the treatment of *ulcerative colitis*. It must be clearly understood that no cures were produced, nor is there a reasonable expectation of cure from such therapy. The cases stud-

ied were all of long standing and showed little effect from all other methods of therapy, which should not be interrupted or displaced by the use of liver. The series numbered but 8 cases, all of whom demonstrated reduction in the number of stools, decrease and disappearance of pus and blood, improvement in the bowel lesions (as seen by sigmoidoscopy and roentgenography), gain in weight, and more satisfactory evacuations (*i. e.*, the replacement of the characteristic watery frequent movements by less frequent, formed stools). The *dosage* outlined was 10 units given intramuscularly 3 times weekly for 1 month, then twice weekly for 1 month, then once weekly for 1 month, thereafter the dose being regulated by necessity. It is Cheney's belief that the active agent is neither the contained vitamin B<sub>1</sub> or B<sub>2</sub> nor the G-fraction of Cohn. In the Reviewer's experience it is evident that there is much more present in liver extract than the antipernicious anemia principle. Highly refined products with the highest antianemic rating permitted by the Council (15 units per cubic centimeter) are not always as effective as the less-refined and lower-rated extracts.

Certainly the anorexia which accompanies ulcerative colitis, the impaired absorption occasioned by the pathologic changes, and the constant drain due to the frequent watery evacuations might easily lead to the belief that part of the picture of this clinical entity may be in the nature of a deficiency disease. While there is no unanimity of opinion or observation, liver extract is worthy of trial in ulcerative colitis. The dosage outlined should not be strictly adhered to, it is a common experience in the treatment of Addisonian anemia that patients using the same liver preparation may differ widely in their liver extract require-

ments, and similar adjustment should be made in its use in this connection.

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### METRAZOL

(Cardiazol; Pentamethylenetetrazol)

**Metrazol Shock Therapy**—The use of *epinephrine hydrochloride* (1:1000 solution) given intravenously immediately prior to metrazol shock therapy reduces the dose of metrazol required to one-half.<sup>16, 17</sup> The extreme cyanosis formerly associated with metrazol shock is greatly decreased, and the degree of apnea is somewhat lessened.<sup>16</sup> The technique is as follows: 0.5 cc. of 1:1000 solution of epinephrine hydrochloride is given intravenously; at the moment of facial blanching, 4 cc. (one-half the average dose) of metrazol is administered by vein. Those who have used this combined method report fewer "missed convulsions."

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### NICOTINIC ACID

Nicotinic acid has been used in the treatment of *radiation sickness*. In a series of 70 cases recently reported by Graham,<sup>18</sup> of Toronto, 74.3 per cent were improved, *i. e.*, vomiting ceased and nausea disappeared or was greatly decreased. Doses of 1½ to 3 grains (100 to 200 mg.) are given 3 times daily, the powder being dissolved in ½ glassful of water and taken slowly over a half-hour period to minimize the subjective sensations of warmth and tingling. These results compare most favorably with the more commonly employed barbiturates or parenteral liver therapy.

Good effects have been ascribed to nicotinic acid in the treatment of the *nausea and vomiting accompanying sulfonamide therapy*. Attempts have been made to evaluate this so-called anti-toxic effect of nicotinic acid and there has been a wide divergence of results.

These discrepancies may, perhaps, be due to the presence of subclinical deficiency states. No satisfactory explanation can be given at present as to the mode of action of nicotinic acid in these circumstances.

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### PICROTOXIN

Many cases of *barbiturate poisoning* treated with picrotoxin have been reported with recoveries from doses far above the average fatal dose. There is no room for doubt that picrotoxin does produce evidence (muscle twitching, convulsive movements, increased respirations) of stimulation in humans suffering from barbiturate poisoning. There is no proof of the efficacy of picrotoxin as an antidote, but its *cautious* use may be justifiable at the present state of knowledge.

In addition to the usual supportive measures, ⅓ to ⅓ grain (1 to 10 mg.) of picrotoxin may be given intramuscularly or intravenously at 1- to 30-minute intervals until signs of stimulation are noted, and further medication used as indicated by the recurrence and depth of depression, gradually decreasing the dose and lengthening the time interval. While picrotoxin is a powerful convulsant poison, a total dose of 32½ grains (2134 mg.) has been reported<sup>19</sup> despite which the patient died on the eighth day from the ingestion of 500 grains (32.5 Gm.) of barbital sodium. The detoxification, excretion, and side-effects of large doses of picrotoxin in humans is thus far unknown. With careful study of the patient, and cautious use, there is probably little danger to the barbiturate-poisoned individual. The proper place of picrotoxin as an antidote remains yet to be established. It has been suggested that if convulsions supervene, a quickly-acting, and quickly-eliminated bar-

biturate, such as *pentothal sodium*, be employed intravenously.

### PROPADRINE HYDROCHLORIDE

**Description** — Di-phenyl-1-amino-2-propanol-1-hydrochloride;  $\alpha$ -hydroxy- $\beta$ -amino-propyl-benzene hydrochloride;  $C_6H_5.CHOH.CHNH_2.CH_3.HCl$ .

Propadrine hydrochloride is the mono-hydrochloride of one of the ephedrine-like bases, differing from it by the replacement of the methyl group in the amino radical with an atom of hydrogen. It is a white crystalline powder with an odor like that of benzoic acid; freely soluble in water and alcohol; insoluble in ether, chloroform, and benzene. The watery solution does not change litmus.

**Physiological Action and Uses**—In its actions it is similar to ephedrine, but its power of producing vasoconstriction and shrinkage when applied to turgid mucous membranes is claimed to be more prolonged. It is further purported to be lacking in the annoying side-effects which are not uncommonly observed in the use of ephedrine. In the treatment of allergic disease, particularly *angioneurotic edema* and *urticaria*, it gives more relief than ephedrine.<sup>20</sup> In the treatment of acute *asthmatic seizures*, it is no more effective than ephedrine sulfate, but like ephedrine, propadrine hydrochloride is effective in aborting attacks.

**Preparations and Dose**—The available preparations are a 1 per cent aqueous solution and 0.66 per cent jelly for intranasal instillation. In the treatment of allergic manifestations, capsules of  $\frac{3}{8}$  and  $\frac{3}{4}$  grain (0.025 and 0.05 Gm.) are provided. According to the experience of Murphy,<sup>20</sup>  $\frac{3}{4}$  grain (0.05 Gm.) is the more satisfactory starting dose, except in children.

### SULFONAMIDES

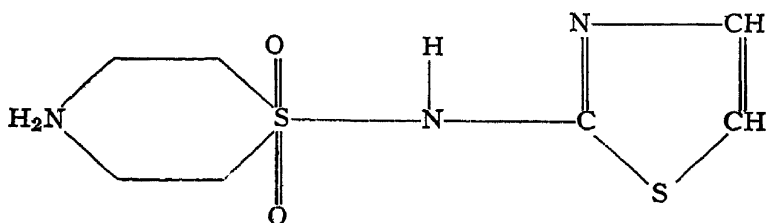
**Introduction**—One of the most significant developments of recent years has been the chemotherapeutic attack on infectious disease. It was in 1908 that Gelmo synthesized para-amino-benzene-sulfonamide, now widely known as sulfanilamide, but it was not until 17 years later, with the advent of Domagk's work on the chemotherapy of bacterial infections, that this new weapon was trained on bacterial aggression.

There has been a whole host of related compounds prepared. Chemists, bacteriologists, and pharmacologists have collaborated in the search for highly effective and relatively nontoxic preparations. The work goes on apace, and the avalanche of literature is almost overwhelming. Kolmer<sup>21</sup> lists over 375 contributions in the bibliography of a recent review. In the present review, remarks will be confined to the 3 sulfonamides which provide the greatest experience upon which to base conclusions, *i. e.*, sulfanilamide, sulfapyridine, and sulfathiazole.

SULFATHIAZOLE

-2-sulfanilamidothiazole

-2(-para-amino-benzene-sulfonamide)thiazole



In 1939, there appeared almost simultaneously reports by Fosbinder and Walter<sup>22</sup> and Lott and Bergheim<sup>23</sup> of the synthesis of a sulfonamide compound, 2 (para-amino-benzene-sulfonamide) thiazole, which has been termed *sulfathiazole*. Since then, Laudon and Sjorgren<sup>24</sup> have claimed priority, referring to Swedish patent 2124, 1939, for details of preparation. Van Dyke and his co-workers found sulfathiazole to be less acutely toxic than sulfapyridine for mice, and more so in chronic studies.<sup>25, 26</sup> It was also noted by this same group of workers that sulfathiazole was absorbed and excreted more rapidly than sulfapyridine, and that the proportion of conjugated sulfathiazole was less in both blood and urine. In the control of experimental pneumococcic infection in mice, the effects of sulfathiazole were found to be comparable to sulfapyridine, but it was more effective in experimental staphylococcic infections. This was also the experience of Barlow and Homburger.<sup>27</sup> Shortly thereafter, Reinhold, Flippin and Schwartz<sup>28</sup> investigated the behavior in humans, using 83 pneumonia patients and 9 controls. They noted also rapid absorption and excretion in the urine, low toxicity, and proportionately low conjugation. After intravenous administration of sodium sulfathiazole, recovery of the drug in the urine was almost quantitative. Absorption *per rectum* was very slight.

Observations on the absorption, excretion, diffusion, and acetylation of sulfathiazole in man were carried out by Sadusk, Blake and Seymour,<sup>29</sup> who noted that in general there was comparatively rapid absorption and elimination of the drug, but that there was rather wide individual variation. These workers also found that there was free diffusion into pleural and ascitic fluid, but very little diffusion into noninflamma-

tory spinal fluids. Spink and Hansen<sup>30</sup> and Sadusk and Nielsen<sup>31</sup> found that sulfathiazole did not diffuse into the spinal fluid in meningitis. Nathanson<sup>32</sup> observed adequate levels in pericardial effusion. The observation of Long,<sup>33</sup> who has had a very extensive experience with sulfonamide therapy, corroborated these findings, and further stated "our experience to date leads us to believe that it [sulfathiazole] is about as effective as sulfapyridine in pneumococcic pneumonia in human beings, and at least as effective as sulfapyridine, if not more so, in staphylococcic infections in man." It was his impression at that time that this new drug produced less nausea and vomiting than would have been expected under sulfapyridine therapy.

Stirling<sup>34</sup> reported the use of sulfathiazole in 2 cases of *septicemia*, 1 due to *staphylococcus aureus*, and 1 of a non-hemolytic streptococcus, with recovery in both instances. Dietel and Kaiser<sup>35</sup> administered sulfathiazole to a 20-months' infant who had a *staphylococcus aureus meningitis* and positive blood culture with complete success.

Spink and Hansen<sup>30</sup> treated 128 bacterial infections of various kinds with sulfathiazole. Among them were 15 successive cases of *staphylococcic septicemia*, all of which recovered. It was their impression that the drug was as effective as sulfapyridine in the therapy of *pneumococcic pneumonia* in the 33 cases studied, and more effective in eradicating *urinary infection* due to staphylococci, *B. coli*, hemolytic streptococci, and *B. proteus*. They also noted rapid absorption and excretion, and believed they observed less nausea and vomiting, and more skin reactions than are produced by sulfapyridine.

The experience in the treatment of 964 cases of *gonorrhea* was given by Miescher.<sup>36</sup> This author thought there

was little therapeutic difference between sulfathiazole and sulfapyridine. He noted that men recovered more quickly than women, and that sulfathiazole was better tolerated.

A comparative study of the effect of sulfapyridine and sulfathiazole in *pneumococcic pneumonia* was made by Flippin, Schwartz and Rose.<sup>37</sup> They treated 100 cases with each agent, and the observations made in this well-controlled series of 200 are worth considering in detail. The corrected mortality rates for sulfathiazole treated patients was 7.4 per cent and for the sulfapyridine group 11.4 per cent. Sulfapyridine appeared to be the quicker-acting drug, because it brought the temperature down more often in the first 24 hours. The incidence of complications was about the same. Total hospital days were the same for both groups, 13.2. The severity and frequency of nausea and vomiting in the sulfathiazole group was much less, and other toxic manifestations were about equal.

Reports by Alyea and Roberts; Carroll, Kappel and Lewis; Cook and others,<sup>38-41</sup> all attesting to the efficacy of sulfathiazole in treating pneumococcic, gonococcic, staphylococcic, and *B. coli* infections, have appeared. The critical evaluation of small series and individual case reports is difficult and would profit little here. There is ample evidence attesting to the fact that sulfathiazole is an effective chemotherapeutic agent, and that its chief indications at the present time appear to be in infections caused by

1. Pneumococci
2. Gonococci
3. Staphylococci
4. *B. coli*

There is evidence at hand, though not as convincing, that it may prove useful in combatting infections due to meningo-

coccus, *Clostridium welchii*, some strains of *Streptococcus nonhemolyticus* and *Streptococcus viridans*.

**Toxicity**—The toxic manifestations are those which experience has shown may be expected from the use of sulfanilamide and sulfapyridine. Nausea and vomiting occur but uncommonly. Vertigo of varying degree may occur, and it is wise to caution ambulatory patients to refrain from hazardous pursuits while undergoing therapy. Drug fever, which usually appears from 5 to 9 days after the beginning of administration, can be most distressing; it should always be considered when the patient who appears to be getting well feels badly and suffers a rise in temperature. The fever curve is not pathognomic and may even resemble that seen in a septicemia, with the accompanying chills, headache, and increased toxicity. Dermatological manifestations vary, and range from simple erythema to marked purpura. Hematuria (microscopic or gross) is not rare and should always be watched for. There is experimental evidence that acetyl-sulfathiazole crystals are deposited in the renal tubules<sup>42</sup> and are highly insoluble. To prevent the occurrence of concretions, it would be well to maintain the daily output above 1000 cc. Two cases of urinary calculi have been reported, the first by Pepper and Horack<sup>43</sup> and the second by Loewenberg and Sloane.<sup>44</sup> It may be noted that in the latter case a total of 1¾ ounces (52 Gm.) of the drug had been administered. The depression of the hematopoietic system by sulfonamides has been well recognized. Thus far, leukopenia and granulocytopenia have infrequently been observed, and but 1 case of agranulocytosis has been reported,<sup>45</sup> but other hematological manifestations of toxicity should not be disregarded. Injection of the conjunctiva

TABLE VI  
(Long, Haviland, Edwards and Bliss<sup>46</sup>)

MANIFESTATIONS OF DRUG TOXICITY NOTED IN HOSPITALIZED ADULTS, 1000 TREATED WITH SULFANILAMIDE, 297 TREATED WITH SULFAPYRIDINE AND 271 TREATED WITH SULFATHIAZOLE

Reaction	Sulfanilamide	Sulfapyridine	Sulfathiazole
Nausea, vomiting .	Fairly common	Frequent	Uncommon
Dizziness .	Common	Common	Uncommon
Psychoses*	0.6 per cent, occur early	0.3 per cent, occur early	Not reported as yet
Neuritis**	Very rare	Not reported	Not reported
Cyanosis	Very common, early and late	Faint, common, early and late	Uncommon
Acidosis* .	1.9 per cent, occurs at any time, rare if soda is used	Not reported	Not reported
Fever* . . . . .	10 per cent, generally fifth to ninth day, may occur first to thirtieth day	4 per cent, generally fifth to ninth day, may occur first to thirtieth day	10 per cent, generally fifth to ninth day
Rash* .	1.9 per cent, may take any form, generally fifth to ninth day, may occur first to thirtieth day	2 per cent, may take any form fifth to ninth day, may occur first to thirtieth day	5 per cent, nodular type common, may take any form, fifth to ninth day
Hepatitis** . . . . .	0.6 per cent, early or late	Not seen, but reported	Not reported
Leukopenia with granulocytopenia** . . . . .	0.3 per cent, early or late	0.6 per cent, early or late	1.6 per cent, early or late
Acute agranulocytosis** . .	0.1 per cent, occurs fourteenth to fortieth day, common seventeenth to twenty-fifth day	0.3 per cent, occurs fourteenth to fortieth day, common seventeenth to twenty-fifth day	Not reported
Mild hemolytic anemia . .	3 per cent, early and late	Rare	Not reported
Acute hemolytic anemia**	1.8 per cent, occurs first to fifth day	0.6 per cent, occurs first to fifth day	Not reported
Hematuria* . . . . .	Not reported . . .	8 per cent, generally early	2.5 per cent, generally early
Anuria with azotemia** .	Not reported	0.3 per cent, generally first to 10 days	0.7 per cent, generally first to ten days
Hyperleukocytosis* .	Generally in presence of acute hemolytic anemia	Generally in presence of acute hemolytic anemia	Not reported
Injection of scleras and conjunctivas* . . . .	Not reported	Not reported	4 per cent, may occur with rash and fever, fifth to ninth day
Purpura hemorrhagica**	Not seen, but reported	Not seen, but reported	Not reported
Ocular and auditory disturbances* . . . . .	Rare	Rare	Not reported
Jaundice** . . . . .	With acute hemolytic anemia or hepatitis	With acute hemolytic anemia or hepatitis	Not reported
Painful joints* . . . . .	Reported	Not reported	Reported with rash, etc.
Stomatitis* . . . . .	Rare	Not reported	Not reported
Gastrointestinal tract disturbances* . . . . .	Bleeding rare, diarrhea uncommon	Rare	Not reported

\*Best to stop drug and force fluids.

\*\*Imperative to stop drug and force fluids.

with burning and lacrimation have been noted.

Long and his associates,<sup>46</sup> who have had an extensive experience with these chemotherapeutic agents, compiled a very interesting table which is reproduced *in toto*. This summarizes part of their observations of the toxic manifestations seen in 1000 adults treated with sulfanilamide, 297 treated with sulfapyridine, and 271 treated with sulfathiazole.

**Description** — Sulfathiazole is a white, odorless, tasteless, crystalline powder which is soluble in glacial acetic acid, pyridine, hot water, *hot* methyl, ethyl, and isopropyl alcohols; slightly soluble in ethyl, methyl, isopropyl alcohols, and very slightly soluble in water at room temperature. The determination of the micro-melting point indicates the presence of 2 crystalline forms, 1 melting at 172° to 173° C., the other at 200° to 203.5° C.

**Dosages and Manner of Administration**—The dosage and manner of administration correspond to that used in the administration of sulfapyridine. An initial dose of 60 grains (4 Gm.) is given to patients with pneumococcic pneumonia, or those who are seriously ill, and this is followed by 15 grains (1 Gm.) every 4 hours, day and night. Dosage should not be arbitrary, but rather guided by the blood level of sulfathiazole. (The method of Bratton and Marshall<sup>47</sup> has proven most suitable for these determinations.) It is to be remembered that there is wide individual variation in absorption and secretion, hence blood levels should be determined daily and dosage adjusted accordingly. Levels above 5 mg. of free sulfathiazole per 100 cc. of blood are deemed satisfactory. An effect should be clearly apparent within 72 hours, and then the dosage reduced to 15 grains (1 Gm.) every 6 hours for 2 days, then to 7½ grains (0.5 Gm.)

every 6 hours for 2 days. At the end of 7 to 10 days the medication may be discontinued. The initial dosage for children (up to 11 lbs.—25 kg.) is calculated on the basis of 2½ grains (0.15 Gm.) per 2½ pounds (1 kg.), and the total daily dose calculated on the same basis.

Used in this manner, the number of relapses will be greatly reduced. Daily blood counts and urinalyses should be performed. Every patient undergoing sulfonamide therapy should be seen at least daily by the physician and due cognizance taken of toxic manifestations. Rise in temperature between 4 and 9 days of therapy should suggest the possibility of drug fever as well as the onset of possible complications.

The combined use of *specific antiserum and sulfathiazole or sulfapyridine* in the treatment of *pneumococcic pneumonia* is a much disputed one. Theoretically, better results would be expected from the use of both than from either alone, for the antiserum will increase the immune antibody content of the blood, while chemotherapy exerts mainly a bacteriostatic effect. Finland, Spring, Lowell and Brown<sup>48</sup> made this the subject of study but could arrive at no definite conclusions. The use of the skin test with specific pneumococcus polysaccharide, as proposed by Francis, may be of great value in clarifying the situation and enabling a clear-cut decision to be made. Lord, Robinson and Heffron<sup>49</sup> recommend combined therapy according to the following criteria:

1. When treatment is begun after the third day of the disease.
2. In patients 50 years of age and over.
3. When pneumococcus bacteriemia is known to be present.
4. When involvement of more than 1 lobe is present.
5. In patients who are pregnant or in the first week of the puerperium.



6. If there is no obvious improvement within 18 to 24 hours after the inauguration of drug treatment, but this interval may be prolonged to 24 to 36 hours in the absence of conditions 1 to 5 above.

It is thought well to accompany *sulfathiazole with sodium bicarbonate* administration in almost equivalent doses, since this may deter acetylation and hence tend to reduce the incidence of renal calculi. Barlow and Climenko<sup>50</sup> have shown that the administration of the alkali (sodium bicarbonate) also hastens absorption from the gastrointestinal tract. If hematuria should appear, the drug should be stopped and fluids forced. If necessary, drug administration may be resumed with great caution. If hematuria reappears, it is best to discontinue its use altogether.

### Sulfapyridine Sodium

Sulfapyridine sodium, the monohydrate salt of sulfapyridine (2-sulfanilaminopyrine) has been accepted by the Council on Pharmacy and Chemistry of the American Medical Association for inclusion in New and Nonofficial Remedies.<sup>51</sup> Aqueous solutions of this drug are strongly alkaline, and therefore must be given intravenously. It is used in 5 per cent solution in sterile distilled water, and administered very slowly by vein (12 to 15 minutes being consumed). In the blood the sodium ion is split off, leaving sulfapyridine. The action, toxicology, and therapeutic indications are essentially those of sulfapyridine. This preparation merely presents a parenteral method of administration for those patients in whom peroral administration is impossible, but this is rarely the case. As soon as it is feasible, parenteral administration should be discontinued and peroral medication begun. The dosage is about the same as sulfapyridine, 60 grains (4 Gm.) given intravenously in

a 5 per cent solution in sterile distilled water. It never should be combined with any other fluids or medicaments. When continued, doses of 15 grains (1 Gm.) may be given at 4- to 6-hour intervals. Venous thrombosis is apt to occur where repeated injections are given. As in all sulfonamide therapy, dosage should always be guided by blood levels and due consideration for toxic manifestations.

### Sulfanilamide

While much literature is available, little of unusual significance has appeared in regard to sulfanilamide therapy. The Council on Pharmacy and Chemistry of the American Medical Association<sup>52</sup> reports sulfanilamide to be of value in the treatment of infections caused by Lancefield group A hemolytic streptococci, the salivarius and mitis strains of alpha-hemolytic streptococci except in subacute bacterial endocarditis, meningococcus, gonococcus, *Clostridium welchii*, *B. coli* infections of the urinary tract; and of dubious value in Brucella infections, chancroid, trachoma, lymphogranuloma venereum.

It would be well to take cognizance of the work of Osgood and others<sup>53-55</sup> with experimental infection of human marrow cultures and the effect of chemotherapy thereon. From their observations it may be deduced that neoarsphenamine and sulfathiazole are effective against staphylococcus aureus infections, that sulfapyridine is only slightly effective, and that sulfanilamide is ineffective. Similar studies made with infections of alpha-hemolytic streptococci (*streptococcus viridians*) showed great variation in the effect of sulfapyridine, sulfathiazole, neoarsphenamine, and mapharsan against various strains, but sulfanilamide is relatively ineffective. Using the same methods in determining the effect of sulfapyridine with and without type-specific

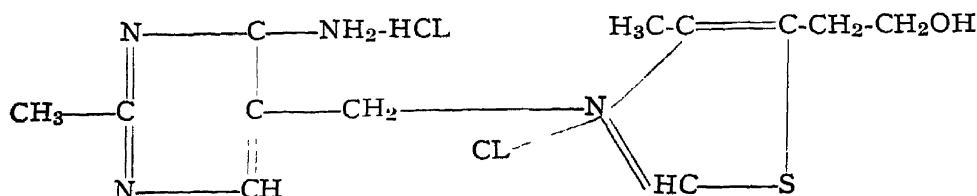
antiserum in pneumococcic infection, better results are indicated from their combined use than from either alone. If, as it appears, there is close correlation between this experimental method of study and actual clinical results, it may well

repeated in 12 to 24 hours if necessary, but this is unusually the case.

## THIAMIN HYDROCHLORIDE

### Description—

(Vitamin B<sub>1</sub>)



provide the key to unlock a conquering horde of specific chemotherapeutics. The eventual results must be weighed in the balance of experience and tested by the acid of time.

## THEOPHYLLINE WITH ETHYLENEDIAMINE (Aminophylline)

The increasing use of theophylline with ethylenediamine (aminophylline) is evidence of the beneficial effects obtained by physicians.

A sterile solution containing  $3\frac{3}{4}$  to  $7\frac{1}{2}$  grains (0.24 to 0.5 Gm.) of theophylline with ethylenediamine may be given intravenously with advantage to patients suffering from so-called *epinephrine-fast bronchial asthma*. The solution should be injected slowly through a narrow gauge (No. 21 or No. 23) needle to avoid unpleasant reaction. Care must be exercised to avoid perivascular infiltration. It often has been noted that after the use of aminophylline as indicated, the efficiency of epinephrine has been restored. The mechanism responsible for this phenomenon is not understood. Relief is usually obtained within 20 minutes. The same dosage may be

Thiamin hydrochloride occurs as white crystals or white crystalline powder with a yeast-like odor, and a somewhat salty taste. It is soluble in water 1:1, glycerin 1:20, alcohol (95 per cent) 1:100, and insoluble in ether and benzene. It is comparatively stable in the dry state, and melts at about 245° C., with resulting decomposition. It is destroyed when exposed to the action of alkalis, sulfites or the dioxide of sulfur. In aqueous solution it is acid in reaction to litmus.

The recognition of beriberi as a deficiency disease is credited to the Japanese naval officer, Takaki, as early as 1884. Eijkman in 1897 demonstrated that rice polishings contained the active material which would prevent the development of beriberi. Since then many men, especially Fund, Williams, Seidell, Jamsen and Donath worked on the problem of securing concentrated, highly potent materials from rice polishings by many chemical procedures, and attempted to arrive at the chemical formula for the antineuritic vitamin. Finally, in 1937, Cline, Williams, and Finkelstein described the synthesis of crystalline vitamin B<sub>1</sub>.

Its natural occurrence in foods is widespread, and has been noted previously. Those interested will find its content in foods classified in Technical Bulletin Number 707 of the U. S. Department of Agriculture, December, 1939.

In passing it is well to emphasize the fact that this vitamin is water-soluble, and consequently there is apt to be great loss through discarding the water in which vegetables are cooked, the milling of wheat flour, and the polishing of rice.

**Physiology**—The effects of thiamin chloride are determined by depriving the experimental animal of vitamin B<sub>1</sub>, observing the changes resulting therefrom, and noting the reversal obtained by administering the drug.

The outstanding manifestation of thiamin chloride lack is the development of polyneuritis. Histological examination reveals degeneration of the myelin sheaths of all peripheral nerves in varying degree. Degenerative changes are also, but less often, noted in the ganglion cells of the brain, spinal cord, and dorsal roots. Selfridge has observed demyelination of the acoustic nerve in rats and chicks, producing nutritional deafness.

That B avitaminosis produces cardiac failure was noted by Wenckebach. Soma Weiss has emphasized this in several communications.<sup>56</sup> This clinical entity is characterized by elevation of the pulse rate, marked cardiac enlargement, dyspnea on exertion, a circulation time which is normal or more rapid than normal (this phenomenon is sometimes noted in patients suffering from thyrotoxic heart disease), elevated venous pressure, increased pulse pressure, diminished vital capacity, and may or may not be accompanied by edema. It is thought by some that the edema in these cases may very well be purely of nutritional origin, *i. e.*,

dependent in large measure on alteration of serum albumin and globulin. Abnormal electrocardiographic patterns are the rule, but changes are not characteristic or pathognomonic.

The gastrointestinal manifestations are rather well known. Anorexia is an early and very common finding, the cause of which is obscure. Sparks and Collins demonstrated by roentgenography decrease in intestinal motility and loss of colonic tonus. Animal experiments, in the intact animal, seem to corroborate this. On isolated intestines, thiamin has no apparent effect.

Studies of the effects of vitamin B<sub>1</sub> deficiency on the endocrine glands of experimental animals have yielded only controversial results, many of the findings reported being of a nonspecific nature.

Vitamin B<sub>1</sub> is regarded as being significantly and intricately related to carbohydrate metabolism. There is little doubt that if the proportion of carbohydrate is increased in a diet deficient in B<sub>1</sub>, symptoms will be provoked more rapidly. There is definite evidence that B<sub>1</sub> in the form of its pyrophosphate is necessary for the oxidation of pyruvic acid and indirectly, of lactic acid, suggesting that the vitamin functions as a coenzyme, cocarboxylase. Its effect (known as the catatorulin effect) is to increase the oxygen uptake of tissues suffering from B<sub>1</sub> depletion, and it thus serves as an intracellularly active enzyme. It is commonly accepted that fats (in high fat diets) "spares" vitamin B<sub>1</sub> and decreases the requirement, as opposed to a high carbohydrate intake which increases need.

**Dosage**—Cowgill<sup>57</sup> postulates a formula for determining the human requirement.

$$\frac{\text{Vitamin B}_1 \text{ requirement (in milligram equivalents)}}{\text{Total caloric intake}} = 0.284 \text{ weight (kg)}$$

[One milligram equivalent of the crystalline vitamin B<sub>1</sub> hydrochloride is 0.05 International Units or, conversely, 1 International Unit equals 20 mg. equivalents (Cowgill). To convert these values into terms of crystalline thiamin chloride, it is to be remembered that 1 mg. is equal to 333 International Units.] This formula is questioned. It is difficult to realize why an obese individual requires more vitamin B<sub>1</sub> to metabolize a fixed intake than a slim one. Further, this formula does not take into account differences in the carbohydrate and fat portions of the diet, there evidently being a greater requirement in the former than in the latter.

The Council on Pharmacology and Chemistry of the American Medical Association states: "The daily requirement for vitamin B<sub>1</sub> appears to be not less than 50 I.U. for the infant and 200 I.U. for the adult." The optimum intake has not as yet been defined. Inasmuch as no toxic phenomena have as yet been reported for man, despite the intravenous administration of as much as 150 mg. daily (49,500 I. U.) it would be well to adopt in practice a somewhat higher standard of from 1.0 to 2.0 mg. daily for maintenance (333 to 666 I. U.).

While vitamin B<sub>1</sub> is probably less adequately supplied in the average American diet than any of the other food factors known at this time, deficiency is further promoted by many factors which are tabulated by Jolliffe.<sup>58</sup>

#### FACTORS INCREASING THE VITAMIN B<sub>1</sub> REQUIREMENT

##### I. INCREASE IN TOTAL METABOLISM:

A. Abnormal activity, as associated with:

1. Prolonged strenuous activity.
2. Delirium.
3. Manic-depressive psychosis, manic type.

B. Fever, especially of long duration, as in:

1. Tuberculosis.
2. Typhoid.
3. Malaria.

C. Hyperthyroidism.

D. Pregnancy.

E. Rapid growth.

##### II. FAULTY ASSIMILATION:

A. Diarrhea, especially of long duration, as in:

1. Ulcerative and mucous colitis
2. Intestinal parasites.
3. Intestinal tuberculosis
4. Sprue.

B. Gastrointestinal fistulas.

C. Diseases of liver or gall-bladder.

D. Achlorhydria.

E. Carcinoma of stomach.

##### III. INCREASED EXCRETION:

A. Polyuria, as in:

1. Uncontrolled diabetes mellitus.
2. Diabetes insipidus.
3. Long-continued excessive fluid intake, as in urinary tract infections.

B. Lactation.

As can be judged from the preceding statements, dosage requirements are uncertain, and it seems best to err on the side of generosity. Crystalline thiamin hydrochloride may be given orally, intramuscularly, or intravenously. For seriously ill patients it is recommended that doses of 20 to 50 mg. be given divided into 2 or 3 doses daily by the intramuscular or intravenous route. This may be continued for 10 to 14 days, and then be replaced by the same dosage given orally. When all symptoms attributed to vitamin B<sub>1</sub> deficiency have disappeared, a daily dose of 1 to 2 mg. may be employed to reinforce the diet. It is well to note that dietary deficiencies unusually occur singly, and in all cases it is well to prescribe an adequate and satisfactory dietary regimen.

Thiamin chloride is absorbed from both the large and small bowel, with very marked variation, depending on

bowel content, bowel motility, and the kind of food ingested. It is eliminated in the feces in negligible quantity, and Harris and Leong estimated the urinary loss at from 5 to 8 per cent of the daily intake.

Biological and chemical methods for quantitative determination of vitamin B<sub>1</sub> content and excretion tests are noted,<sup>59,60</sup> which are valuable to the research laboratory, but as yet no satisfactory clinical laboratory test has appeared to detect subclinical states. The need must be determined by the clinician, and evidence offered only by therapeutic test.

**Toxicity**—No reports of acute toxic manifestations have appeared despite comparatively enormous doses. In dogs, 350 mg. per kilogram of body weight given intravenously produced respiratory failure and death. Other toxic manifestations were shock, muscular twitching, and clonic spasms. Similar results appear with doses of 125 mg. per kilogram of body weight for mice, 250 mg. per kilogram of body weight for rats, and 300 mg. per kilogram of body weight for rabbits.

**Therapeutic Indications**—The use of thiamin hydrochloride at present is enjoying the most widespread popularity. Its advantageous therapeutic use, however, must lag behind, borne on the shoulders of controlled observation. It is of primary importance in the prevention and cure of what is still known to many as "oriental" *beriberi*. It may be used with advantage in those who suffer *loss of appetite*. Therapeutic trial is the only means of determination. Employed in certain forms of *heart disease* (see above), particularly in the absence of a "cardiac history," and where there is no apparent response to digitalis, recovery may be complete. Thiamin hydrochloride has a definite place in the

treatment of peripheral *polyneuritides of diabetes, alcoholism, and pregnancy*, its need being gendered not alone by deficiency of diet, but also by derangement of metabolism. In the treatment of gastrointestinal disorders much is said, and little substantiated. Those enterological states in which improvement is reported following B<sub>1</sub> administration probably reflect multiple deficiencies, not alone of diet, but also secondary deficiency states due to impaired digestive and/or absorptive powers. The judicious physician, not being dazzled by the glamour with which the laity endows all vitamins, may find this drug of value in the treatment of some patients, but definition of the type of patient is not possible. Since with increased metabolic states of all kinds, vitamin B<sub>1</sub> need is increased, thiamin may be administered with profit to those suffering from *hyperthyroidism*. Its use in *pregnancy* and during the *growth* period is definitely indicated when consideration of the dietary reveals subnormal intake of vitamin B<sub>1</sub>.

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## VITAMIN E

(Alpha-tocopherol)  
(5, 7, 8-trimethyltolcol)

**Description and Source**—In a study of dietary effect on the ovulatory rhythm and reproduction in rats, Evans and Bishop in 1922 recognized the existence of vitamin E, an accessory food factor without which death of the fetus invariably occurred, and when certain articles of food (fresh lettuce, whole wheat) were added to the diet, normal gestation proceeded. Vitamin E deficiency did not prevent estrus, ovulation, or ovulatory impregnation, but did interfere with normal gestation. Corroboration was soon forthcoming.



application to man and cattle is more by analogy than by actual demonstration.

Vitamin E deficiency leads to muscular dystrophy in rats and guinea-pigs.<sup>63-66</sup> This dystrophy is brilliantly amenable to vitamin E therapy.

Vitamin E and alpha-tocopherol are readily absorbed from the intestinal tract, and present in fat and muscle tissue of animal bodies. That it is well stored is evidenced by the fact that several normal pregnancies may occur before deficiency becomes apparent, despite subsistence on a deficient diet. Pregnancy does not seem to increase the need for or utilization of the vitamin. It is stated that deficiency in E intake sufficiently prolonged will retard growth of rats after about the fourth month.

**Indications**—The therapeutic indications at present are limited to *habitual abortion, muscular dystrophies*,<sup>67, 68</sup> *amyotrophic lateral sclerosis*,<sup>69</sup> but proofs of the curative effects attributed to this vitamin in man are still to be assembled. It would seem that the normal dietary includes adequate vitamin E intake. Nothing as yet can be said with certainty. Those who are considering the use of either wheat-germ oil or alpha-tocopherol in the treatment of habitual abortion would do well to consult the report of the Council on Pharmacy and Chemistry of the American Medical Association.<sup>70</sup>

**Dosage**—The dosage of vitamin E either as wheat-germ oil or alpha-tocopherol has not been established. This is further complicated by wide variation in the potency of wheat-germ oils. Dosages as high as 12 drams (48 cc.) have been employed initially, followed by 1 dram (4 cc.) daily. The parenteral use of alpha-tocopherol has followed 2 plans, (a)  $\frac{3}{4}$  to  $1\frac{1}{2}$  grains (50 to 100 mg.) in oil injected intramuscularly daily, or (b)  $1\frac{1}{2}$  to 5 grains (100 to 300 mg.)

twice weekly. The merits of either or both procedures cannot be ascertained at this time. As yet no practicable biological or chemical methods of assay are available to act as a guide to vitamin E administration.

Idiosyncrasy, gastrointestinal upsets, and cutaneous reactions to alpha-tocopherol injections have been noted. The peanut oil used as a solvent may or may not have been an etiological factor.

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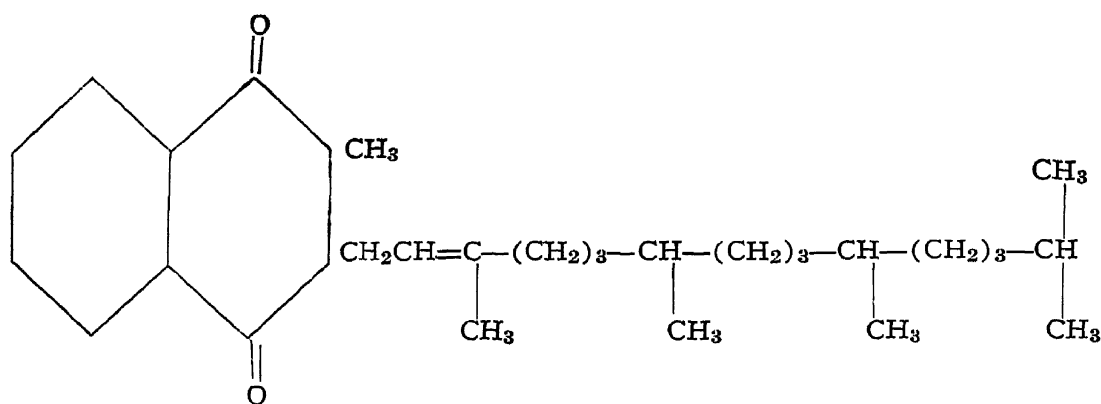
## VITAMIN K

One of the clinically significant additions to the therapeutic armamentarium of specific hemorrhagic tendencies is vitamin K, the so-called antihemorrhagic accessory food factor. Dam, studying sterol metabolism in chicks, noted the development of a marked hemorrhagic tendency associated with deficient plasma prothrombin. The diet supplied to these chicks was, by design, deficient in certain fat-soluble substances, but presumably contained an adequate vitamin supply. The cause of this lowering of plasma prothrombin and consequent tendency to hemorrhage appeared to be a fat-soluble accessory food factor which he named vitamin K (Koagulations). At almost the same time, Almquist and Stokstad reported on a hemorrhagic chick disease of dietary origin. Vitamin K was said by Dam to be the accessory food factor present in certain natural foods which prevented the development of hemorrhagic disease in chicks maintained on a special dietary free of fat with the exception of 1 per cent cod-liver oil. Recently it has been shown that the essential structure of vitamin K is a naphthoquinone, and that there are a number of naphthoquinones which demonstrate the ability to restore the plasma prothrombin level and counteract the effects of the stipulated deficient diet.<sup>71-75</sup>

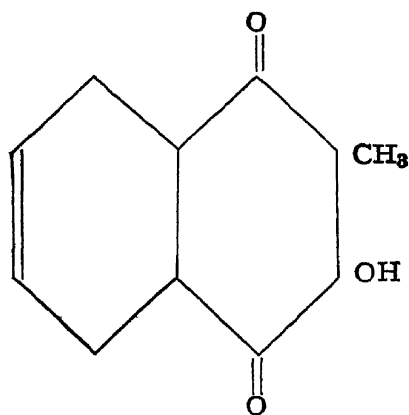
The natural vitamin K is soluble in ether, hexane, and hot methyl alcohol from which it precipitates on cooling. It is present in the chlorophyll-bearing portion of all plants. The best natural sources are evidently alfalfa (Cerophyl, the first available clinical material, was made from dried young cereal plants), soy-bean oil, spinach, rice meal, putrefied fish meal, hemp seed, kale, casein, hog fat, and egg yolk. It is present in the feces of animals fed on vitamin K

deficient diets, being synthesized by intestinal flora (colon bacilli, *Staphylococcus aureus*). Material possessing K activity has been found in the tubercle bacillus, *B. subtilis*, *B. coli*, and *Staphylococcus aureus*.

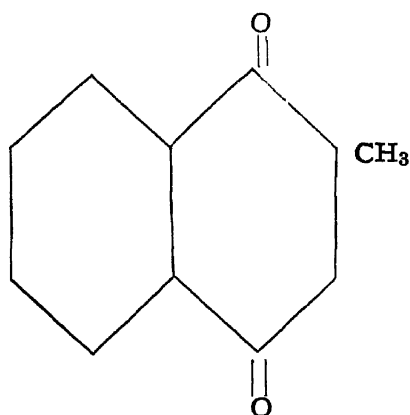
The unit employed by Dam is the least amount of vitamin K per gram of chick per day capable of producing normal coagulability in the blood of a K-avitaminotic chick after 3 days' feeding.



Vitamin K<sub>1</sub> (2-methyl-3 phytyl-1, 4-naphthoquinone)



Phthiocol (2-methyl-3-hydroxy-naphthoquinone)



2-methyl-1, 4-naphthoquinone

The material isolated from alfalfa in Doisy's laboratory and designated vitamin K<sub>1</sub> was shown to be 2-methyl-3-phytyl-1, 4 naphthoquinone. Phthiocol, isolated from the tubercle bacillus was shown to be 2-methyl-3-hydroxy-naphthoquinone. Of the group, the most

potent appears to be 2-methyl-1, 4 naphthoquinone,<sup>72, 76, 77</sup> a synthetic preparation of low solubility which is quite irritating when given into the muscle or under the skin. Andrus and Lord<sup>77</sup> and Macfie, Bacharach and Chance<sup>78</sup> have successfully used 2-methyl-1, 4-naphtho-



quinone dissolved in corn oil and given by intramuscular injection. It seems not unlikely that the latter synthetic preparation will become the standard for potency determination, but at the present time vitamin K is to be assayed in terms of biological activity, and should include any substance capable of correcting the hemorrhagic disease of the avitaminotic chick described by Dam.

The exact rôle to be assigned vitamin K has not yet been determined. Chemical tests thus far devised for it are not capable of detecting it in small enough quantities to determine its metabolism or course *in vivo*, nor are any satisfactory urinary excretion studies available. Studies on normal individuals have been of little service, because despite maintenance on K-free diets, there are nevertheless significant amounts of the vitamin available by intrainestinal bacterial synthesis or degeneration. Another hindrance to further elaboration of its mechanism of action is the incomplete knowledge of blood coagulation. It was only in 1935 that Quick introduced the use of thromboplastin in the estimation of the prothrombin level in plasma, and provided a practicable basis for prothrombin measurement, even though its composition is unknown. It has been demonstrated that the addition of vitamin K to prothrombin deficient plasma will not improve its clotting.<sup>79</sup> Prothrombin levels will be increased only when the vitamin has been metabolized, apparently being utilized by the liver for the formation of prothrombin. The factors influencing the absorption of vitamin K, therefore, become of prime importance as well as the factor of intake.

It has been shown by Andrus, Lord and Moore<sup>80</sup> that the vitamin is without effect in hepatectomized animals. It is also well known that vitamin K is poorly absorbed from the intestine in the ab-

sence of liver bile—this condition being produced clinically by persistent biliary fistula or common duct obstruction. Absorption of vitamin K in such cases will follow the administration of whole bile (recovered by biliary drainage by duodenal tube), bile concentrates, or any of several bile salts, the most effective being sodium deoxycholate. It thus appears that bile products serve as an intermediary vehicle for the transition through the intestinal wall in much the same manner as they serve for carotene and the fat-soluble vitamin D. The absorption chiefly takes place in the small intestine, and inadequate absorption has been reported in marked intestinal derangements occasioned by sprue, celiac disease and intestinal fistula.<sup>81</sup> From these remarks, it readily may be understood that the liver plays here a dual rôle, *i. e.*, (1) providing bile to admit of the absorption of the vitamin from the intestine, and (2) synthesizing prothrombin. Severe liver damage (by poisoning with hepatotoxic agents, such as carbon tetrachloride and chloroform; by disease, as in acute yellow atrophy or cirrhosis) will thus produce lowering of plasma prothrombin levels which will not respond to the use of bile and vitamin K.

In summary, the hemorrhagic tendency noted in certain conditions is produced by decrease in plasma prothrombin; this decrease may be due to liver failure or to K avitaminosis; in man this avitaminosis may be due to:

(1) Inadequate intake over a long period of time.

(2) Intestinal derangement which prevents absorption; or

(3) Usually, and most important, failure of vitamin K absorption because of absence of bile products in the small intestine.

**Toxicity and Contraindications—**Vitamin K has, as yet, demonstrated no

recognized evidence of toxicity. Ruigh<sup>82</sup> states that 10,000 times the therapeutic dose of 2-methyl-1, 4-naphthoquinone may produce hemolytic anemia in animals. The use of any of the vitamin K preparations is contraindicated as being useless in all cases of hemorrhagic disease due to factors other than prothrombin deficiencies.

**Plasma Prothrombin Estimation—**Quick's method of determination enjoys wide use. This is based on the proposition that if thromboplastin and calcium are added in optimum quantity to blood which enjoys normal fibrinogen quantity, the factor which prolongs the time necessary to form a clot is prothrombin deficiency. The degree of deficiency is proportionate to the increased time required for clotting. Ziffren and his co-workers<sup>83</sup> have proposed a simple bedside method for testing prothrombin content:

Place 0.1 cc of thromboplastin (prepared from tissue extract) in a 3 cc. test-tube to which 1 cc. of freshly drawn blood is immediately added; the tube is inverted and tilted gently until the clot forms and the time required for coagulation noted; the same procedure is repeated on a normal individual and the unknown calculated in percentage of the normal thus:

$$\text{Clot activity in per cent of normal} = \frac{\text{coagulation time of normal individual}}{\text{coagulation time of patient}} \times 100$$

Dam and Glavind<sup>84</sup> use a method whereby heparin plasma is clotted by tissue extract in a series of increasing concentrations, and that concentration producing clot in 3 minutes is recorded. This concentration is compared to the concentration necessary to produce clot with a normal plasma treated in the same manner, thus:

$$\text{Clotting activity (c)} = \frac{\text{normal concentration}}{\text{patient's concentration}}$$

The danger levels (below which there may be hemorrhage) vary with the dif-

ferent methods used for determining prothrombin levels, and therefore it is best to use the same method routinely.

**Therapeutic Use—**Vitamin K is of therapeutic benefit only in conditions where there is depression of plasma prothrombin levels and where hepatocellular damage is not so marked as to render prothrombin anabolism impossible. It is of no avail in purpura hemorrhagica, hemophilia, and other blood dyscrasias. It sometimes may be indicated by greatly increased prothrombin times in *leukemia*, and *prolonged, severe infections*. Its most widely accepted application is confined to the *hemorrhagic diathesis* present in the jaundice accompanying hepatic and biliary disease, in those in whom duodenal drainage (by indwelling tube and suction) is long continued, and for the less frequent cases of *K avitaminosis* due to faulty diet or absorption by reason of intestinal derangement. It will not increase the speed of clotting when the plasma prothrombin is normal, nor will it counteract the effects of heparin.

A vitamin K preparation should be administered to all *jaundiced patients on whom surgery is contemplated* even though there is little significant

depression of prothrombin levels. Response is usually prompt and in 24 to 36 hours levels approximating normal are achieved. Oral administration is quite satisfactory and intramuscular injection should be employed on those who by reason of intragastric hemorrhage, marked distention, intestinal obstruction, repeated vomiting, or the use of Wangenstein drainage, cannot take the drug by mouth. Its use in jaundiced patients should be continued postoperatively, and when discontinued, it is well to repeat-

edly check prothrombin levels until the patient is taking an adequate dietary, and biliary flow into the intestine has been established. This may be overlooked in patients with a drainage tube implanted into the common duct, with a consequent fall in plasma prothrombin, and may result in dire consequences.

When *active hemorrhage* is present, treatment becomes more difficult. *Blood transfusion* is definitely indicated, not only to combat shock, but to supply prothrombin directly. For this reason, stored or "bank" blood should never be used, since it has been demonstrated that the prothrombin content of stored blood rapidly diminishes.<sup>85, 86</sup> *Vitamin K* may be given parenterally where material is available, otherwise oral administration *with bile salts* should be instituted.

It has been repeatedly noted that the prothrombin time of newborn infants is considerably longer than that of normal adults. In this regard, Hellman and Shettles<sup>87</sup> showed that by giving vitamin K to pregnant females 2 to 4 weeks before delivery, there was a significant rise in the infant's plasma prothrombin. Many others<sup>88-94</sup> have corroborated this, and on the basis of this work it may be recommended that vitamin K be administered to mothers late in pregnancy, and to infants during the first 2 weeks of life as a means of *preventing hemorrhagic disease of the newborn*. Since there is, in these cases, presumably adequate biliary flow into the intestines, there is no indication for the use of a bile salt. In the cases studied, no untoward results have been reported, the vitamin being administered either in the formula, as supplementary feedings, or by injections of a water-soluble preparation.

**Dosage**—The dose, manner of administration, and frequency of administration are controlled by the condition

of the patient and by repeated determination of the plasma prothrombin levels. The water-soluble dihydroxy derivative of phthiocol, and 4-amino-2-methyl-1, 4-naphthol hydrochloride have been suggested for intravenous use. Experience with this route is, at the present, limited and reports are not available. Suitable dosage at this time would seem to be by oral administration:

Cerophyl—37½ to 75 grains (2.5 to 5.0 Gm.)  
3 times daily  
Klotogen—10 grains (0.6 Gm.) 3 times daily  
2-methyl-1, 4-naphthoquinone— $\frac{1}{65}$  grain (1.0 mg.) 3 times daily.

These dosages are in excess of the required maintenance dose which is less than  $\frac{1}{65}$  grain (1.0 mg.) of 2-methyl-1, 4-naphthoquinone daily.

Intramuscularly, 2-methyl-1, 4-naphthoquinone may be given in a concentration of 1.0 mg. per cubic centimeter of corn oil<sup>5</sup> in which it is suspended. This preparation is sterilized by autoclaving at 20 pounds pressure for 1 hour, and is put up in 2 cc. ampoules. The usual dosage is 2.0 mg. (20 cc.) given deep intramuscularly, and may be repeated at intervals of 3 days. By this method an effect is noted by the end of 8 hours and the action is prolonged.

When a vitamin K preparation is being employed by mouth, it should be accompanied by appropriate bile salts or its derivatives to provide for its absorption. Suitable preparations are: Bilron, 10 grains (0.6 Gm.); sodium taurocholate and glycolate, 15 to 30 grains (1.0 to 2.0 Gm.); deoxycholic acid, 3 grains (0.2 Gm.); sodium deoxycholate, 3 grains (0.2 Gm.), given 3 times daily with the vitamin.

## ZINC PEROXIDE

The use of zinc peroxide in the treatment of chronic undermining, burrowing

*ulcers* is receiving more attention. Meleney has largely been responsible for stressing the importance of anaerobic cultures made routinely (as well as aerobic) in revealing the presence of microaerophilic hemolytic streptococci, which readily yields to peroxide of zinc therapy. According to Shallow, Fry, and Pulaski,<sup>95</sup> who corroborate the original work, 3 rules must be adhered to if success is to attend this mode of therapy:

1. The zinc peroxide must be potent.
2. The freshly prepared suspension must be in intimate contact with all parts of the injected surface.
3. The dressing must be *effectively* protected against evaporation and drying.

The revised method of application, once the presence of the organism has been proven, as presented by Meleney and Harvey,<sup>96</sup> may be briefly outlined:

1. Sterile zinc peroxide powder is mixed intimately with sterile distilled water to make a 40 per cent cream.
2. The cream is widely and *carefully* spread to assure good contact.
3. Dressings are renewed daily.
4. Sulfanilamide is given orally in the usual dosage.
5. If areas of activity persist after 1 week's treatment, the ulcerated, active areas should be excised and therapy continued. If the application of the zinc peroxide to fresh surfaces is productive of pain, this may be ameliorated largely by flushing the wound with 2 per cent *novocain* and then reapplying the zinc peroxide cream.
6. When the ulcerated areas are thoroughly clean, small deep *grafts* are used as necessary, zinc peroxide being applied over the sealed dressing of the grafts.
7. When epithelization has begun, and anaerobic cultures fail to yield hemolytic streptococci, 0.5 per cent *oxyquinoline* in 5 per cent *scarlet red ointment* may be substituted to stimulate epithelial growth and wound closure.

This procedure promises much in terminating successfully long-standing, distressing, and eventually incapacitating

lesions. Its successful application will reward painstaking care.

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## UROLOGY

*Edited by P. S. PELOUZE, M.D.*

### CYSTOSCOPY AND RENAL DIAGNOSIS

*By BRANSFORD LEWIS, M.D., B.Sc., AND GRAYSON CARROLL, M.D.*

The diagnosis of urologic conditions in infants and children has been greatly facilitated by the improved small cystoscopes, which permit thorough investigation of the smallest infant. Correction of valves, bars, and tight ureters prevents adult pathology. Children tolerate instrumental treatment very satisfactorily. Intramuscular urography has recently been practiced in infants who have small or sclerosed veins. The injection into the gluteal muscle of 17 to 35 per cent diodrast is the accepted procedure. *Wilms' tumors, hydronephrosis, and horseshoe kidney* have all been successfully diagnosed by this method.

*Pneumoroentgenography*,<sup>1</sup> the injection of air (400 cc.) into the perirenal space, has been practiced by some and that combined with retrograde urography has been advocated.

The *air pyelogram*<sup>2</sup> in localization of stone prior to operation, and the *air ureterogram*, to identify papillary growths and calculi not opaque in the roentgenogram, are becoming popular with some urologists. These measures should be reserved for only the most obscure cases, since air embolii have been reported in some few cases. For many years, Bransford Lewis has identified nonopaque stones by injecting 25 per cent *argyrol*, and after it has drained away, a roentgenogram shows a faint

shadow of the colloidal substance adherent to the stone.

*Medication concretions*<sup>3</sup> are a new form of deposits now observed in the kidney and ureters. The first clinical case in this country was reported by Carroll and Shea in 1938, following the use of *sulfapyridine*. *Sulfathiazole* concretions are now being reported, the latter appearing in the tubules of the kidney, while the former are observed in the calyces, pelvis, ureter, or bladder. The following observations may be tabulated concerning these facts.

1. Urinary concretions during the administration of sulfapyridine and sulfathiazole may cause *urinary obstruction*, partial or complete.

2. The condition is detected by decreased urinary output, and cloudy urine caused by blood and crystals. The concretions are not opaque to the x-ray. The nonprotein nitrogen becomes elevated; the concentration of the drug in the blood is increased.

3. The treatment is to ***discontinue the drug, force fluids*** by mouth and intravenously in the form of ***glucose***. If this is not successful, ***cystoscopic lavage of the renal pelvis with hot saline solution*** is usually effective.

The more recently recognized observations in *differential diagnosis of kidney lesions* may be briefly mentioned. A pic-

ture of the spider-like narrowed calyces with the small pelvis and irregular outline of the kidney is the typical *tumor pyelogram*. A single calyx narrowed or bowed with a smooth bulging border may be a *solitary cyst*. Bilateral narrow calyces with a large kidney shadow, together with low specific gravity of urine and poor renal function, are found in *polycystic kidneys*, which are always bilateral. The dilated pelvis and obliteration of calyces with a sharp angle of the ureter at the ureteropelvic junction strongly suggest an *aberrant renal vessel* crossing under the ureter. Absence of dye in this area is also noted. Adhesions or stricture may simulate this picture. *Cortical abscess* of the kidney, which is usually staphylococcal, may be detected by the widening of the area between the upper and middle, or middle and lower, calyx, narrowing of the calyx, or pelvis, or bowing of these structures. Fever, deep tenderness and leukocytosis accompany this condition, but the urine may be free from pus, only showing staphylococcus in the culture.

Moth-eaten, feather-edge pyelograms, with shagginess or slight distortion of usually an upper calyx, are invariably indication of *tuberculosis*. Culture smear or guinea-pig inoculation substantiates the findings. A beaded ureter portrays either *tuberculosis* or *uretera cystica*.

The *perinephritic abscess* is detected by the absence of the psoas shadow, the

bowing of the spine, the tender area about the size of a dollar in Petit's triangle, and fever.

The pyelogram with calyces pointing medially (nonrotated kidney) is strongly suggestive of a *horseshoe kidney*, the isthmus being made more evident by intravenous urography with injection of air.

The introduction of the *cystometer*, made popular by Rose,<sup>4</sup> has greatly stimulated the study of the *neurogenic bladder*, differentiating the tabetic, the hyperplastic, and paralytic type. Surgical relief has been obtained in some of these by *removing the presacral ganglion* and the *parasympathetic nerves* or *transurethral resection of the internal sphincter*.

The method of recording the movements in the human intact ureter, introduced by Trattner, has enhanced knowledge concerning pathologic conditions and has made possible the study of the effect of certain drugs on the ureter. Ockerblad noted that morphine caused contraction of the ureter and atropine neutralized this action. Carroll, Grayson and Zingale<sup>5</sup> demonstrated by the kymograph that *pancreatic tissue extract* relaxed the ureter and introduced it for relief of *renal colic*. Increased mobility was observed when 1:4000 *prostigmine* was injected intramuscularly, this knowledge being used clinically by Vincent O'Connor<sup>6</sup> in expelling *ureteral calculi*.

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## GONORRHEA IN THE MALE

By P. S. PELOUZE, M.D.

**Treatment with Sulfonamide Compounds**—Recent studies and a correlation of the former clinical results obtained in the treatment of gonorrhea in

the male with sulfonamide drugs have brought out a great many valuable facts that do much to place the chemotherapy of this disease on a higher plane.

1. Sulfanilamide does not cure gonorrhea in more than 30 per cent of ambulatory cases. It has a high carrier and toxicity rate.

2. Sulfapyridine carries a higher apparent cure rate (60 to 90 per cent) according to different authors whose work contains few points for criticism. Dose for dose, it is about as toxic as sulfanilamide. It apparently produces fewer carrier states.

3. Sulfathiazole compares therapeutically with sulfapyridine but is less toxic.

4. High blood concentration is insignificant so far as urogenital gonorrhea is concerned. It may be important in the systemic metastases, though this has not been shown to any great extent.

5. If a sulfonamide drug is going to influence gonorrhea favorably in the male, it renders the patient symptom-free within 5 days of the beginning of its administration.

6. If it is going to cure, it does so in 10 days or less and administration of the same sulfonamide for longer periods increases the number of toxic side reactions as well as wastes expensive drugs.

7. Sulfapyridine and sulfathiazole commonly produce favorable results in patients classed as sulfanilamide failures but the reverse is not true.

8. It has been thought desirable to allow from 3 to 5 days to elapse between the use of one sulfonamide and another. Such a view, however, rests upon clinical judgment and not upon scientific proof.

9. For definite drug failures and proved carrier states where rotation from one sulfonamide to another fails to eradicate infection, local treatment occupies the sole consideration toward the promotion of cure.

10. The steady trend has been toward lower dosage and shorter periods of medication and in Chart I is to be seen

the dosage schemes employed by some of the most careful investigators.

It should be realized that in those patients influenced by sulfonamide drugs, the symptoms disappear usually within the first 72 hours. There being, then, no urethral discharge, the 2-glass test is only of negative value and ordinary microscopic study of smears is not possible. It is well to be impressed with the negative value of the 2-glass test in all its features in such cases. Most assuredly it does not in any way indicate cure, for it has been shown statistically regarding sulfanilamide that if a clear urine for 2 weeks or longer is viewed as a criterion of cure, persisting infection will be missed in 1 of 3 patients. If to this negative 2-glass test are added careful microscopic searches for the gonococcus, 1 of 20 cases will have an undetected carrier state. If to both of these are added careful cultural studies, only 1 of 100 persisting infections will escape detection.

Thus, in tests of cure, cultural studies assume a place of the utmost importance if carriers are not to be passed back into their former activities. For it must be remembered that many patients erroneously assumed to be cured can indulge in all of the things so potent in reproducing symptoms in nonsulfonamide cases without the least recurrence of symptoms. This causes doubt in all cases even though cultural studies are employed. Such studies are not as generally available as the need demands and many patients could not afford the cost if they were. Also, there are clinical obstacles to their general use; the percentage of positive findings rapidly reduces as the time increases between obtaining the material for culture and the plating of this material. In other words, the patient and the laboratory must be in close proximity. It cannot be said, further, that all such



cultures are made in a way to give the most reliable results. Many diagnoses are made by the oxidase test on the plate growth alone and this test is not sufficiently selective to justify the bacteriologist in pronouncing a colony gonococcal just because it turns pink and then black

an unfortunate group of conditions presents a real hazard for the physician, the patient, and, particularly, for his later sexual partners. And he who makes careless pronouncements frequently will have much to regret. The production of asymptomatic carrier states should be

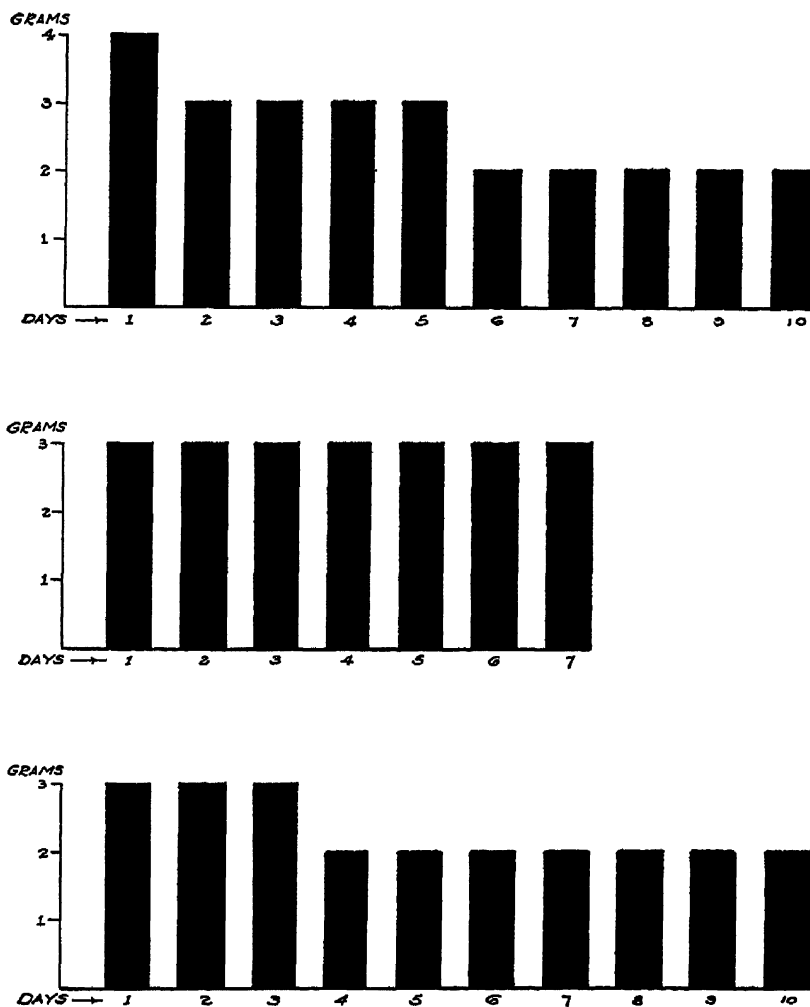


Chart I—Schemes of sulfonamide dosage used by some careful investigators with approximately similar results.

when the test solution is poured on the plate. Beyond this, the older fermentation tests should be employed for the differentiation of the various *Neisseriae* and in many laboratories this is not done.

Hence, it is easily seen that there is much to be done before the ideal is reached so far as ability to make even a good guess at cure is concerned. Such

kept in mind by the physician to the end that he gives instructions for the most careful studies of all such exposed persons.

The limitations of cultural studies as well as their widespread lack of availability urge that a far better type of microscopic study be indulged in than heretofore. These are not beyond the

skill of any laboratory worker or any physician with even a superficial knowledge of laboratory work. Indeed, they are so simple that there is little need for their neglect in most offices or communities. Their reliability is not absolute, but by the use of the following procedures, they are almost as valuable as cultures. At least, the writer has not had a single later positive culture or recurrence in any patient upon whom these studies failed to reveal the gonococcus. This, however, does not of necessity prove that some infected patients have not escaped discovery.

Seemingly cured patients have no urethral discharge and they have a clear urine. If the gonococcus is present, it probably is either in the prostate, Cowper's glands, or the urethral follicles and secretions must be obtained from these structures. Also, the obtained fluids must be subjected to a technic that makes for thin spreads that will adhere to the slide. This can be done in the following way:

1. Strip the urethra, from the perineum out, rather firmly, strip the prostate and Cowper's glands, and then have the patient pass about  $\frac{1}{2}$  ounce of urine into a beaker.
2. Throw down the sediment from the urine in a centrifuge.
3. Invert the centrifuge tube quickly, to pour off the supernatant urine—the sediment will remain in the tip of the tube.

4. Partially fill the tube with normal salt solution and shake the sediment into suspension

5. Centrifugate again and pour off the salt solution as in number 3.

6 Obtain the material for study from the tip of the still inverted centrifuge tube with either a platinum loop or a small cotton-wrapped applicator.

7 Spread thinly on the slide and stain by the Gram method.

If cultures are to be made, a portion of the urine can be sent to the laboratory for that purpose. By its centrifugation the bacteriologist obtains excellent material for cultural studies and, if too much time has not elapsed, these should be extremely valuable aids if properly carried out.

Finally, no matter how convinced the physician may feel regarding cure, he is foolish to convey his confidence to his patient. It is far better to tell him the whole truth and, for the protection of others and his own peace of mind, to insist that he refrain from sexual intercourse without the use of a condom, proved to be a good one by forcible inflation, for at least 3 months. Few sexually busy individuals will do so for that length of time, but, if mistakes are made, the physician is not left in so vulnerable a situation as would otherwise be the case.

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## PYELITIS AND PYELONEPHRITIS

By WILLIAM E. LOWER, M.D.

1. **Internal Medication**—When relief of the acute symptoms has been secured, urinary antiseptics may be employed. To date, a single ideal urinary bactericide for internal use is not available. Numerous drugs have been enthusiastically propounded but few have stood the test of time. *Mandelic acid*

and the *sulfonamides* seem to be superior to any other excretory antiseptics so far available. Of the older antiseptics, perhaps only *methenamine* should be considered as effective. This drug is inexpensive, nontoxic, and can be administered in large quantities without injury. While methenamine itself is not bacteri-

cidal, the formaldehyde which it liberates in an acid urine is an efficient germicide. A  $pH$  below 5.6 must be maintained if a sufficient amount of formaldehyde is to be generated. The utilization of the high acid-ash *diet* and the oral administration of *sodium acid phosphate* or *sodium benzoate* will help to render the urine acid if the urine does not contain alkaline-producing organisms. As formaldehyde is irritating to the kidney, it is unwise to administer methenamine in the very acute cases of *pyelonephritis*. It is necessary to give not less than 60 grains (4 Gm.) a day of the methenamine and acidifier.

With the introduction of mandelic acid, sulfanilamide, "neoprontosil," sulfa-pyridine and sulfathiazole, the management of *pyelonephritis* has been placed on a strictly scientific basis. For the first time specific drugs have been available for specific treatment of bacterial infections in the kidney. A thorough bacteriological study of the urine is necessary, as the specificity of these various drugs for certain bacteria and even for particular strains of the same bacterium is now evident.

**Mandelic Acid**—Introduced in 1935, this remedy has been shown to be bactericidal for most kidney infections caused by the *Streptococcus faecalis* and from 75 to 80 per cent of colon bacillus infections. Mandelic acid may be utilized when *Escherichia coli*, *Aerobacter aerogenes* and *Streptococcus faecalis* are isolated from the urine. Members of the genera *Salmonella*, *Pseudomonas*, and *Shigella* may respond to this therapy. *Staphylococcus*, *Streptococcus*, and *Proteus* infections rarely are affected by mandelic acid.

Numerous preparations of mandelic acid are available in both liquid and solid form. The elixir of the *ammonium salt of mandelic acid* containing 28 per cent

of the salt is perhaps the most palatable of the liquid preparations. This is usually administered in 3 fluidrams (12 cc.) after meals and at bedtime, giving a total of approximately 3 drams (12 Gm.) of the ammonium salt.

Tablets of *calcium mandelate*, *ammonium mandelate* and a preparation containing *mandelic acid and ammonium chloride* in combination also are efficacious. The dosage approximates that given above for the ammonium salt of mandelic acid.

Certain conditions must exist if the maximum results are to be obtained with this therapy. The  $pH$  of the urine must be maintained between 5.3 and 5.5, the concentration of the drug in the urine must be between 0.9 and 1.0 per cent, and the fluid intake must be restricted to 1000 cc. a day. Mandelic acid is strikingly ineffective when the necessary acidity or the proper concentration cannot be maintained. If the required  $pH$  is not obtained with the administration of mandelic acid alone, *ammonium nitrate* or *ammonium chloride*,  $7\frac{1}{2}$  grains (0.5 Gm.), 4 times a day, should be added. These ammonium salts should not be given in the presence of an organism that splits urea, as the alkalinity of the urine containing this type of organism cannot, as a rule, be changed by the administration of acid-producing drugs, and there is also the danger of calculus formation. The *acid-ash diet* also may be used in conjunction with *mandelic acid* to obtain the proper acidity of the urine. Daily determinations of the urinary  $pH$  should be made. The acidity of the urine may be tested easily with nitrazene paper and the nitrazene colorimeter. As the mandelic acid is eliminated almost entirely in the urine, the concentration of the drug in the urine may be determined from the urinary output over a 24-hour

period and the amount of drug ingested daily.

Mandelic acid is somewhat irritating to the kidney and should not be given when there is any evidence of renal insufficiency. Elderly persons and those with a tendency toward acidosis do not tolerate the drug well.

**Sulfonamides** — With the introduction of prontosil (azosulfamide) in 1935, the search for the ideal urinary antiseptic came a step closer to realization. From this discovery has come a long list of sulfonamide compounds, chief of which are sulfanilamide, sulfapyridine, and more recently, sulfathiazole.

**Prontosil** (azosulfamide) was used extensively at first until it was found that **sulfanilamide** (para-amino-benzene-sulfonamide) was excreted and was probably the active principle; therefore, this drug came into more general use. Sulfanilamide has been found to be bactericidal, both *in vivo* and *in vitro*, for hemolytic streptococci, *Escherichia coli*, *Aerobacter aerogenes*, and *Proteus ammoniae*. It is effective in only a few strains of the staphylococcus but is comparatively ineffective in killing the *Streptococcus faecalis*.

There has been much confusion over the prescribed dosage of **sulfanilamide**. Long<sup>7</sup> and Vest,<sup>8</sup> pioneers in the field of the sulfonamides, suggest a dosage of from 45 to 75 grains (3 to 5 Gm.) of sulfanilamide a day with restriction of fluids to 1200 cc. daily. The best results have been obtained with the following dosage: 60 grains (4 Gm.) a day for a period of 3 days; for the next 2 days, a total dosage of 40 grains (2.65 Gm.) is given. After this period, a maintenance dosage of from 30 to 40 grains (2.0 to 2.65 Gm.) a day for a total period of 10 to 14 days is prescribed. The drug should be administered at regular intervals over the 24 hours to main-

tain in the blood a free sulfanilamide level of approximately 8 to 10 mg. per 100 cc. of blood. In infants, 5 to 10 grains (0.3 to 0.6 Gm.) are given daily; in children from 2 to 5 years of age, 15 grains (1.0 Gm.) daily; from 5 to 10 years of age, 15 to 20 grains (1.0 to 1.3 Gm.) daily; and over 15 years of age to young adults, 20 to 25 grains (1.3 to 1.6 Gm.) daily. Fluids are not restricted in either adults or children. However, Alyea<sup>9</sup> states that a dose of 28 grains (1.8 Gm.) of sulfanilamide a day is as efficacious in the treatment of infections of the kidney as is the large dosage usually advocated. Alyea also is against the restriction of fluids, as he feels that a concentration bactericidal *in vitro* is not necessary *in vivo*.

Oral administration of the drug is the method of choice unless the patient has nausea and vomiting, is comatose, or otherwise critically ill. In this event, an 0.8 per cent solution of sulfanilamide in physiological saline may be given subcutaneously. Dosage corresponds to the figures given above. It has been the practice of the writer to give equal doses of **sodium bicarbonate** with the **sulfanilamide** in an effort to prevent acidosis.

**Azosulfamide** in tablet form, termed "**neoprontosil**" by its manufacturers, also may be utilized in pyelonephritis. This drug, as stated above, forms sulfanilamide in the body by a process of reduction. Its greatest use is in mild infections in which the patient will not tolerate sulfanilamide. A dosage of 40 to 60 grains (2.65 to 4.0 Gm.) should be given daily for at least 10 to 14 days. Fluids are not restricted and it is unnecessary to give sodium bicarbonate with this drug.

**Sulfapyridine**, a compound formed by the coupling of a pyridine ring with sulfonamide benzol, has been used in the treatment of kidney infections, but it ap-

pears to be no more effective than sulfanilamide. Moreover, the acetyl derivative of sulfapyridine, formed by conjugation within the body, is poorly soluble, causing it to precipitate in the form of crystals. These may injure the kidney or form concretions in the urinary tract.

**Sulfathiazole**—The most recent of the sulfonamide compounds to be used in the treatment of pyelonephritis is sulfathiazole. Helmholz<sup>10</sup> showed this compound to be bactericidal for 6 of the most common bacteria found in kidney infections. The effectiveness of the drug for the various bacteria on an ascending scale was found to be as follows: *Pseudomonas aeruginosa*, *Streptococcus faecalis*, *Escherichia coli*, *Aerobacter aerogenes*, *Proteus ammoniae*, and *Staphylococcus aureus*. Pool and Cook<sup>11</sup> report 65 per cent cures among 15 patients with colon bacillus infections, 7 with *Streptococcus faecalis* and 5 with *Staphylococcus aureus*. All of the 5 with staphylococcal infestations were cured. Long<sup>12</sup> is not enthusiastic concerning the use of sulfathiazole in *Streptococcus faecalis* infections of the kidney, and many authors agree that it is contraindicated in the presence of the enterococcus. The writer has used sulfathiazole in a few cases of pyelonephritis in which *Staphylococcus aureus* or *Proteus ammoniae* was the causative organism. Results have been most gratifying. The drug is definitely indicated when either of these two organisms can be isolated from the urine.

The dosage of either sulfapyridine or sulfathiazole is 15 grains (1 Gm.) every 6 hours. The patient is urged to consume at least 2500 cc. of fluids daily. If these drugs cannot be tolerated orally, a 5 per cent solution of the sodium salt in sterile distilled water can be administered intravenously. An initial dose of 60 grains (4 Gm.) may be given, to be followed by 30 grains (2 Gm.) every 12

hours, or 15 grains (1 Gm.) every 6 hours.

A high blood level of free sulfapyridine or sulfathiazole does not appear to be essential for a cure. Blood levels should be calculated, however, at regular intervals, as most of the patients who develop toxic manifestations have been shown to have high blood levels. An optimum level of 5.0 mg. per 100 cc. of blood for sulfathiazole and 7.0 mg. per 100 cc. for sulfapyridine should not be exceeded.

*Toxic Reactions with Sulfonamides*—The incidence of toxicity in patients taking any of the sulfonamides makes it imperative that they be observed closely. Neoprontosil causes fewer reactions than the other 3 preparations discussed. Depression of the bone-marrow resulting in *agranulocytosis* or *leukopenia* has been noted as has *hemolytic anemia*. These complications call for immediate stoppage of the drug and treatment of the complications. Sulfapyridine and sulfathiazole have a tendency to form solid aggregates in the urinary tract which may cause gross or microscopic *hematuria* or a *decreased output of urine*. If the urinary output falls below 1000 cc. a day, the drug should be discontinued.

The more common toxic reactions noted are *nausea and vomiting*, *dizziness*, *headache and mental confusion*. *Drug fever* as well as *dermatitis* may occur. Patients receiving a sulfonamide should not be exposed to ultraviolet rays, as this enhances the chance of a dermatitis. A toxic reaction which seems to be peculiar to treatment with sulfathiazole is *congestion of the conjunctivae and sclerae*. Blood counts, urinalysis and blood-level studies of free compounds should be done at regular intervals.

It has become the routine of the writer to start a patient on the drug which is believed to be most suitable to

the type of infection present in the kidney. If there is no response in 3 or 4 days, the drug is changed to one of the other sulfonamide compounds or to mandelic acid, depending on the organism and the individual.

2. **Vaccines**—The use of either stock or autogenous vaccines has yielded unimpressive results, though they are often worth trying in certain chronic cases.

3. **Instrumental Measures** — In acute infections, the use of instruments, as a rule, is contraindicated. If the patient, however, shows no tendency to spontaneous recovery or experiences considerable pain in the flanks, with evidence of obstruction, it may be necessary to pass a *ureteral catheter* to permit better drainage.

The *in-dwelling ureteral catheter* is useful at times, particularly in those cases complicated by obstruction. The catheter should not be left in place for more than 24 hours. During this time frequent *lavage* may be carried out. The alternative is repeated lavage at intervals of several days, this method finding its greatest usefulness in the chronic and ambulatory cases.

Numerous solutions may be used for lavaging the kidney pelvis, *i. e.*, *silver nitrate* in 1 or 2 per cent solution; *argyrol*, 4 to 10 per cent; *acriflavine*, 1:2000; *aluminum acetate*, 0.25 per cent; *sulfanilamide*, 0.8 per cent; *sulfanilamide maltoside*; "*neoprontosil*" 2.5 to 5 per cent; and an *aqueous solution of merthiolate*, 1:10,000.

## LABORATORY UROLOGY AND STATUS OF RESEARCH

By RUSSELL DORR HERROLD, B.S., M.D.

1. **Gonorrhea**—Since the introduction of the sulfonamide drugs, the carrier state has assumed increasing importance. After a favorable clinical response from the more potent sulfanilamide derivatives, such as sulfapyridine and sulfathiazole, the patient may remain asymptomatic for periods varying from weeks to months. Unfortunately, during this period of time such patients may be refractory to activation by the recognized provocative tests, and microscopic study of spreads of the various exudates may not reveal typical gonococci. Repeated negative cultures are necessary to assure bacteriologic cure. Fortunately, there are now available more simplified and reliable methods of cultivating the gonococcus. A simplified, basic medium has been developed together with a sterilizable enrichment, which has proved quite satisfactory even for the smaller labora-

tories. The composition of the basic medium is as follows:

Difco proteose-peptone No 3....	40 Gm.
Dextrose ... ..	1 Gm.
Sodium chloride .....	10 Gm.
Disodium phosphate . . . . .	10 Gm.
Agar .....	30 Gm.
Distilled water .....	1000 cc.

To the above medium an equal quantity of 2 per cent bacto-beef hemoglobin in distilled water is added after the agar is melted. The efficacy of cultures can be increased further by incubation of the plates in airtight containers after the addition of 10 per cent carbon dioxide. It is important to suspend the suspected exudates in nutrient broth before inoculation onto the solid mediums. Also, if the specimens cannot be inoculated promptly, they should be kept in the ice-box in the interim between collection and inoculation. The oxidase test as de-

scribed by Gordon and McLeod has proved helpful in identifying the gonococcus colonies in the mixed cultures as yielded from specimens that are inoculated during the period of the determination of cure. The test is made by pouring over the plates a 1 per cent aqueous solution of dimethyl para-phenylenediamine hydrochloride, and observing the color reactions from pink to maroon to black. Smears are made from the pink colonies and examined after the Gram stain. Other gram-negative diplococci giving similar reactions are seldom found in the urinary tract. The small percentage of false reactions by other bacteria are rarely confusing because there is a clear-cut morphological differentiation.

**2. Nonspecific Infections of Urinary Tract**—Since the differentiation of the various gram-negative bacilli is needed in order to select the most suitable medication, the use of eosin methylene blue agar is recommended as an additional medium to plain and blood agar. Hemoglobin agar as described for the cultivation of the gonococcus is quite satisfactory for the fastidious growing bacteria of the urinary tract. Green streptococci may be differentiated from anhemolytic streptococci. While it is not satisfactory as a criterion of hemolysis, beta-hemolytic streptococci seldom are found in the urinary tract. Cultures for determination of cure in nonspecific infections of the urinary tract are not reliable until several days have elapsed after the discontinuance of the sulfonamide group of drugs.

The importance of the urea-splitting bacteria of the urinary tract as an etiological factor in calculous disease has been stressed by many investigators during the past few years. While proteus ammoniae has been known to be a strong alkalinizer, little attention has been given to this ability of many strains of the

staphylococcus group, as well as some of the gram-negative bacilli other than proteus. The writer has found that a simple and reliable method of determining the presence and degree of urea-splitting bacteria is the incubation of the specimens of urine from 48 to 72 hours. To approximately 1 cc of incubated urine is added 1 drop of thymol blue indicator solution. A resultant blue color indicates a pH above 8.5 by strong urea-splitting bacteria.

**3. Tuberculosis in Urinary Tract**—Herrold and Woolsey<sup>13</sup> have demonstrated that the intracutaneous route of inoculation of tuberculous exudates frequently shortens the time in which a positive diagnosis can be made in guinea-pigs. Tubercle bacilli were recovered from the lesions in more than half of the guinea-pigs within a period less than 22 days. There have been several publications confirming the value of egg-yolk agar as a medium for the successful cultivation of tubercle bacilli. Recently, Karlson<sup>14</sup> reported 96.8 per cent showing growth of tubercle bacilli on egg-yolk agar as compared to 67.7 per cent growth on a coagulated egg and potato-water medium. Furthermore, growth was detected in an average of 3.4 weeks on the egg-yolk agar, while growth could not be readily detected before 5 weeks of incubation on the coagulated egg and potato-water medium. While this comparison was made from animal tissues, it suggests the need for further observations on egg-yolk agar as a medium for cultivation of tubercle bacilli from the urinary tract.

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